



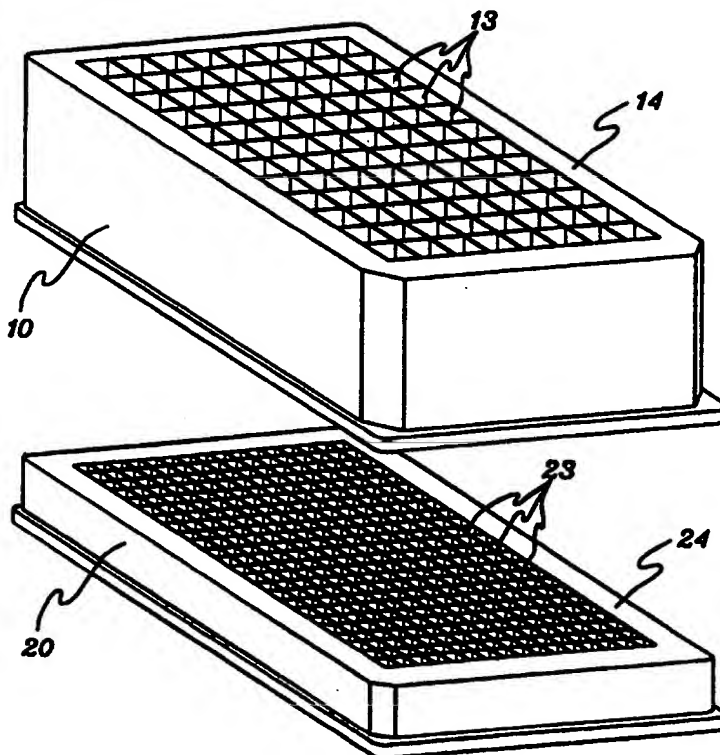
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(54) Title: **ALIGNED MULTIWELL MULTIPLATE STACK AND METHOD FOR PROCESSING BIOLOGICAL/CHEMICAL SAMPLES USING THE SAME**

## (57) Abstract

Device and method for processing biological, biochemical or chemical samples are provided wherein a first multiwell plate (10) is stacked atop a second multiwell plate (20). Each well of the x wells of the first multiwell plate (10) has an outlet (16) at a lower surface (of the first plate (10)). The second multiwell plate (20) has y wells arranged in a regular array, each well of the y wells (23) being capable of receiving a separate sample, and wherein (Y) > x. The outlets (16) at the lower surface of the first multiwell plate (10) are arrayed to register sealingly with corresponding inlets of a subset of the y wells (23) of the second multiwell plate (20) when the first plate is stacked atop the second plate. A mechanism for aligning the first plate to the second plate is provided, as well as transfer indicia for tracking transfer of sample.



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ALIGNED MULTIWELL MULTIPLATE STACK AND METHOD FOR  
PROCESSING BIOLOGICAL/CHEMICAL SAMPLES USING THE SAME

Technical Field

5 This invention relates in general to biological, biochemical and chemical assays, and more particularly, to a sampling and filtration device comprising a stack of multiwell plates which is useful in processing such assays.

Background Of The Invention

10 Multiwell test plates used for isotopic and non-isotopic in-vitro assays are well known in the art and are exemplified, for example, by those described in U.S. Patent Nos. 3,111,489; 3,540,856; 3,540,857; 3,540,858; 4,304,865; 4,948,442; and 5,047,215.  
15 Typically, such test plates have been standardized in the form of the so-called micro-titre plate that provides, in one example, 96 depressions or cylindrical wells of about 0.66 cm in diameter and 1.3 cm deep, arranged in a 12x8 regular rectangular  
20 array spaced about 0.9 cm center-to-center.

Selected wells in such a test-plate are used to incubate respective microcultures, followed by further processing to harvest the incubated material. Each well typically includes a filtration element so  
25 that, upon application of a vacuum to one side of the plate, fluid in each well is expressed through the filter leaving solids, such as bacteria, debris and the like, entrapped in the well. In typical use, specimens from up to 96 different individuals may be  
30 respectively inserted in corresponding wells in the multiwell plate in the course of an assay, the

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specimens typically all being inserted prior to filtration and completion of the assay.

Oftentimes, it is necessary to transfer biological/chemical samples from one multiwell test plate to another multiwell test plate. The conventional approach to transferring samples is to pipette the samples from the first test plate to the second test plate. However, this approach can be time consuming and difficult depending upon the plate configurations between which samples are being transferred. For example, micro-titre plates providing 384 or 864 cylindrical wells arranged in a regular rectangular array have recently become available. Since each well of a 96-well plate can hold 400  $\mu$ l or more of sample, while a well of a 384-well plate can only hold, for example, 100  $\mu$ l of sample, it is conventionally necessary to pipette sample from each well of the 96-well plate to four different wells of the 384-well plate. Obviously, this procedure can be tedious.

With the availability of the new multiwell plates, various assay processing enhancements are desirable. In particular, enhancements in the transfer process are needed for moving samples from, for example, a 96-well plate to a 384- or 864-well plate. The present invention is directed to providing these processing enhancements for the transfer of samples between different multiwell plates.

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Disclosure Of The Invention

Briefly summarized, this invention comprises in a first aspect a device for processing biological, biochemical or chemical samples comprising a first multiwell plate and a second multiwell plate. The first multiwell plate has  $x$  wells arranged in a regular array, each well of the  $x$  wells being capable of receiving a separate sample, and wherein each well of the  $x$  wells has an outlet at a lower surface of the first multiwell plate. The second multiwell plate has  $y$  wells arranged in a regular array, each well of the  $y$  wells being capable of receiving a separate sample, and wherein  $y \geq x$ . The outlets at the lower surface of the first multiwell plate are arrayed to register with corresponding inlets of  $x'$  wells of the  $y$  wells of the second multiwell plate when the first multiwell plate is stacked atop the second multiwell plate, wherein  $x' = x$ . A means for aligning the first multiwell plate to the second multiwell plate is also provided so that the  $x$  wells of the first multiwell plate automatically align to the  $x'$  wells of the second multiwell plate when the first multiwell plate is stacked atop the second multiwell plate using the alignment means. Samples can be directly transferred from the  $x$  wells of the first multiwell plate to the  $x'$  wells of the second multiwell plate. As an enhanced aspect, the means for aligning may comprise alignment indicia disposed on the first multiwell plate and corresponding alignment indicia on the second multiwell plate, and/or an alignment guide coupled to either the first multiwell plate or the second multiwell plate so that the  $x$  wells of the first multiwell plate automatically align to the  $x'$  wells of the second

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multiwell plate when the plates are stacked using the alignment indicia and/or guide.

In another aspect, the invention comprises a device for processing biological/chemical samples which includes a first multiwell plate and a second multiwell plate. The first multiwell plate has x wells arranged in a regular array, each well of the x wells being capable of receiving a separate sample, and the second multiwell plate has y wells arranged in a regular array, each well of the y wells also being capable of receiving a separate sample. The device further includes transfer indicia for tracking transfer of sample from the first multiwell plate to the second multiwell plate. The transfer indicia, initially disposed within the x wells of the first multiwell plate, may comprise an inert color indicia which automatically transfers to the second multiwell plate upon transfer of samples from the x wells of said first multiwell plate to wells of said second multiwell plate.

In another aspect, the invention comprises a method for processing biological, biochemical or chemical samples comprising: providing a first multiwell plate having x wells arranged in a regular array, each well of the x wells being capable of receiving a separate sample; providing a second multiwell plate having y wells arranged in a regular array, each well of the y wells being capable of receiving a separate sample; providing transfer indicia within at least one well having sample therein of the x wells of the first multiwell plate; and transferring sample from the first multiwell plate to the second multiwell plate, the transferring

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including transferring the transfer indicia from the at least one well of the first multiwell plate to at least one well of the second multiwell plate, wherein the transfer indicia tracks transfer of sample from the at least one well of the first multiwell plate to the at least one well of the second multiwell plate for monitoring possible cross-contamination of wells of the second multiwell plate.

To restate, various techniques are provided herein for directly transferring samples from a first well plate having a first number of wells to a second well plate having a second number of wells, wherein the second number of wells is equal to or greater than the first number of wells. Preferably, the second number of wells is a multiple of the first number of wells. As a specific example discussed herein, the first well plate may comprise a 96-well plate and the second well plate a 384-well plate. Significant time and processing complexity is saved by being able to directly transfer between two different multiwell plates. For example, pipetting apparatus is unnecessary to accomplish the transfer.

In addition to direct transfer of samples between well plates, a technique is provided herein to prevent cross-contamination between wells of the receiving plate, as well as to prevent drying of open wells within the receiving plate. In accordance with the principles of this invention, the first well plate may comprise a filter plate so that simultaneous transfer and filtering of samples occurs during the movement of samples from the first well plate to the second well plate. Further, the second well plate can comprise a chromatographic media so

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that purification of the sample can also simultaneously occur with transfer of the sample from the first well plate into (and through) the second well plate. In accordance with the principles of this invention, a greater volume of sample in the first well plate than can be accommodated in the second well plate can be simultaneously filtered in the first well plate, transferred from the first well plate to the second well plate and purified in the second well plate, before being discharged. Various further advantages, enhancements and examples of processings in accordance with this invention are described further herein.

For example, an alignment mechanism comprising alignment indicia and/or an alignment guide can be provided on either or both of the first multiwell plate and the second multiwell plate. The alignment indicia may comprise positional indicia such as matching color indicia at appropriate corners of the first multiwell plate and the second multiwell plate to facilitate alignment of the outlets of the first multiwell plate to a desired subset of wells of the second multiwell plate. Alternatively, the entire first multiwell plate could be color coded to match color coding on the second multiwell plate to facilitate alignment of the outlets of the first multiwell plate to the desired subset of wells of the second multiwell plate.

Advantageously, the invention also contemplates the use of inert transfer indicia, such as inert color indicia, within the wells for tracking transfer of sample from the wells of the first multiwell plate to the wells of the second multiwell plate. This



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transfer indicia can confirm proper transfer of samples from the x wells of the first multiwell plate to corresponding wells of the second multiwell plate, as well as indicate whether cross-contamination of samples has occurred between wells of the second multiwell plate. For example, different 96-well plates may have different colored transfer indicia which should be transferred with the samples thereof into a corresponding subset of wells of a 384 well plate. Cross-contamination is thus visually identifiable by verifying accuracy of the colors within the wells of the 384 well plate.

#### Brief Description Of The Drawings

The above-described objects, advantages and features of the present invention, as well as others, will be more readily understood from the following detailed description of certain preferred embodiments of the invention, when considered in conjunction with the accompanying drawings in which:

Fig. 1 is an exploded isometric view of a multiwell multiplate stack in accordance with the principles of this invention;

Fig. 2 is a further exploded isometric view of the multiwell multiplate stack of Fig. 1 showing the lower surfaces of the multiwell plates;

Fig. 3 is a plan view of the upper surface of the 96-well plate of the embodiment of Figs. 1 & 2;

Fig. 4 is a plan view of the lower surface of the 96-well plate of the embodiment of Figs. 1 & 2;

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Fig. 5 is a plan view of the upper surface of the 384-well plate of the embodiment of Figs. 1 & 2;

Fig. 6 is a plan view of the lower surface of the 384-well plate of the embodiment of Figs. 1 & 2;

5        Fig. 7 is an isometric view of the multiwell multiplate stack in accordance with the principles of the present invention;

Fig. 8 is a partial cross-sectional view of one embodiment of the multiwell multiplate stack of Fig. 7 showing a first 96-well plate 10 disposed over a first set of wells of the 384-well plate;

Fig. 9 is a partial cross-sectional view of one embodiment of the multiwell multiplate stack of Fig. 7 showing a second 96-well plate 10' disposed over a second set of wells of the 384-well plate;

Fig. 10 is a plan view of the upper surface of the 384-well plate showing an alternate sealing mechanism employing an O-ring and a puncturable membrane across the upper surface of the 384-well plate;

Fig. 11 is a cross-sectional view of Fig. 10 taken along line 11-11;

Fig. 12 is a fragmentary, enlarged cross-sectional view of one embodiment of a well of a 384-well plate in accordance with the present invention containing a purification or separation media;

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Fig. 13 is a fragmentary, enlarged cross-sectional view of a drip director 16' of an upper well plate configured to mesh with an inlet 23" of a corresponding well of a lower well plate in a multiwell multiplate stack;

Fig. 14 is a plan view of the upper surface of one embodiment of a vacuum manifold configured, for example, to receive the lower surface of the 384-well plate of the stack of Fig. 7;

Fig. 15 is a cross-sectional view of one embodiment of the multiwell multiplate stack of Fig. 7 disposed atop the vacuum manifold of Fig. 14 in accordance with the present invention;

Fig. 16 is an isometric view of an alternate embodiment of the multiwell multiplate stack in accordance with the principles of the present invention wherein an alignment guide is affixed to one corner of the 96-well plate such that the 96-well plate registers with a selected quadrant of wells of the 384-well plate;

Fig. 17 is an isometric view of another embodiment of the multiwell multiplate stack of Fig. 16 wherein the alignment guide affixed to the 96-well plate is disposed at a different corner of the 96-well plate such that the 96-well plate registers with a different quadrant of wells in the 384-well plate;

Fig. 18a is a plan view of the upper surface 14a of a 96-well plate 100a comprising an alternate embodiment of the present invention, this embodiment having transfer indicia within the wells and an

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alignment guide at one corner thereof in accordance with the principles of the present invention;

Fig. 18b is an isometric view of the 96-well plate 100a of Fig. 18a;

5        Fig. 18c is an isometric view of the 96-well plate 100a of Figs. 18a & 18b stacked 400a atop a 384-well plate 200 for transfer of sample from the 96-well plate to the 384-well plate in accordance with the present invention;

10       Fig. 19a is a plan view of the upper surface 14b of an alternate embodiment of the 96-well plate 100b of Figs. 18a-18c wherein a different colored transfer indicia is disposed within the wells of the 96-well plate and the alignment guide is disposed at a  
15       different corner for aligning the wells thereof to a different quadrant of wells in the 384-well plate in accordance with the principles of the present invention;

20       Fig. 19b is an isometric view of the 96-well plate 100b of Fig. 19a;

25       Fig. 19c is an isometric view of the 96-well plate 100b of Figs. 19a & 19b stacked 400b atop a 384-well plate 200 for transfer of sample from the 96-well plate to the 384-well plate in accordance with the principles of the present invention;

Fig. 20a is a plan view of the upper surface 14c of another embodiment of the 96-well plate 100c of Figs. 18a-18c wherein a different colored transfer indicia is disposed within the wells of the 96-well

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plate and the alignment guide is disposed at a different corner for aligning the wells thereof to a different quadrant of wells in the 384-well plate;

Fig. 20b is an isometric view of the 96-well plate 100c of Fig. 20a;

Fig. 20c is an isometric view of the 96-well plate 100c of Figs. 20a & 20b stacked atop a 384-well plate 200 for transfer of sample from the 96-well plate to the 384-well plate in accordance with the principles of the present invention;

Fig. 21a is a plan view of the upper surface 14d of still another embodiment of the 96-well plate 100d of Figs. 18a-18c wherein a different colored transfer indicia is disposed within the wells of the 96-well plate and the alignment guide is disposed at a different corner for aligning the wells thereof to a different quadrant of wells in the 384-well plate;

Fig. 21b is an isometric view of the 96-well plate 100d of Fig. 21a;

Fig. 21c is an isometric view of the 96-well plate 100d of Figs. 21a & 21b stacked atop a 384-well plate 200 for transfer of sample from the 96-well plate to the 384-well plate in accordance with the principles of the present invention; and

Fig. 22 is a plan view of the upper surface of a 386-well plate having samples transferred thereto from the four 96-well plates of Figs. 18a-21c, wherein the unique color indicia of each 96-well plate has been transferred to the respective quadrant

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of wells in the 384-well plate for tracking proper transfer of samples in accordance with the principles of the present invention.

#### Detailed Description of the Invention

5           Generally stated, this invention comprises a technique for processing samples, such as biological, chemical or biochemical samples wherein a multiplate stack comprising two or more plates is defined, within and through which samples are transferred.

10   **Figs. 1-7** present a detailed example of two multiwell plates employed pursuant to this invention. A first multiwell plate 10 comprises a 96-well plate and a second multiwell plate 20 is a 384-well plate, which has exactly four times the number of wells as the 96-

15   well plate.

          In many operations, it is desirable to transfer fluid from a 96-well plate to a 384-well plate. These operations include, but are not limited to, the transfer of crude plasmid preparation after cell

20   lysis and precipitation of proteins and genomic DNA, which is typically 400  $\mu$ l of material. This culture sample size conventionally requires a 96-well plate since the well volume in a 384-well plate is too small. Further, processing typically requires the

25   transfer of this material to a 384-well plate, which may contain a quantity of between 5  $\mu$ l and 150  $\mu$ l of high capacity anion exchange resin, such as, e.g., Q HyperD 20  $\mu$ m. Transfer of material from a 96-well plate to a 384-well plate is today accomplished by

30   pipetting the samples from the first test plate to the second test plate.

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Since the 384-well plate has exactly 4x the number of well as the 96-well plate, and since the size and aspect ratio of the two plates can be made similar, then in accordance with the present  
5 invention a 96-well plate 10 with flow directors or outlets 16 (Fig. 2) can be produced for direct stacking atop a 384-well plate. The flow directors 16 direct the sample flow from the 96-well plate to one set of wells of the 384-well plate (i.e., one  
10 quadrant of wells). Again, this requires proper sizing and aspect ratio for the flow directors 16 of the 96-well plate to align or register with a respective set or quadrant of wells of the 384-well plate.

15 Pursuant to another feature of the present invention, the 96-well plate 10 can comprise a filter plate so that when stacked atop, for example, a 384-well plate, sample material can be filtered  
20 simultaneous with direct transfer thereof from the 96-well plate to the 384-well plate. Still another aspect of this invention is the concept that samples in the 96-well plate are drawn into and through wells in the 384-well plate. This can be facilitated via an appropriate vacuum manifold coupled to the lower  
25 surface of the 384-well plate as explained further herein. If desired, the 384-well plate may contain a chromatographic media to separate or purify the sample as it is being drawn through the 384-well plate.

30 In accordance with the principles of the this invention, a sealing mechanism, such as gasket 30 (Fig. 2), is preferably provided so that when multiwell plate 10 is stacked atop multiwell plate

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20, material can be transferred from plate 10 to the selected set of wells of the 384-well plate 20 without contaminating or drying out open wells of the 384-well plate, which as noted may contain  
5 purification media. An "open well" comprises a well of the 384-well plate not having a drip director 16 of the 96-well plate aligned therewith when the 96-well plate is stacked atop the 384-well plate.

Referring now more specifically to **Figs. 1-6**,  
10 first multiwell plate 10, comprising a 96-well plate, has a plurality of wells 13 arrayed in a regular rectangular array with openings 12 thereto in an upper surface 14. Each well has a corresponding drip director 16 in a lower surface 18 of the multiwell  
15 plate 10. Similarly, the second multiwell plate 20, which in this example comprises a 384-well plate, has a plurality of wells 23 also arrayed in a regular rectangular pattern each of which has an opening 22 in an upper surface 24 of plate 20. In accordance  
20 with this invention, drip directors or outlets 26 also depend downwardly from a lower surface 28 of plate 20.

As noted, a significant feature of this invention is the ability to transfer material from  
25 plate 10 directly into plate 20 while simultaneously filtering the material. With conventional pipetting this is not possible. Further, because the volume of each well 13 in 96-well plate 10 is conventionally greater than the volume of each well 23 in 384-well  
30 plate 20, this invention teaches the drawing of material into and from the respective wells of the 384-well plate simultaneous with transfer of the material from the 96-well plate. Thus, separation or



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purification of media drawn into a set of wells of the 384-well plate is also simultaneously accomplished with transfer of the samples from the 96-well plate. To restate, this invention provides  
5 for the direct transfer of samples from a first well plate, such as a 96-well plate, to a second well plate, such as a 384-well plate, while simultaneously filtering the sample and purifying the resultant material. This is accomplished notwithstanding that  
10 each well of the 96-well plate 10 might hold 400  $\mu$ l of sample while the receiving well 23 in the 384-well plate 20 might only hold 120  $\mu$ l.

When this process is completed, another 96-well plate can be used to address another set of wells  
15 from the three remaining sets or quadrants of wells in the 384-well plate 20. This is accomplished by aligning the flow directors of this second 96-well plate with the openings of a different set of wells of the 384-well plate. The second 96-well plate can  
20 register, for example, with the appropriate wells by manually aligning the plates, or by employing a set of alignment guides on the respective plates as shown in Figs. 16 and 17 and described below.

Alternatively, an apparatus could be constructed  
25 which allows for four different alignment positions of a 96-well plate over the 384-well plate, or four different 96-well plate embodiments could be configured, each with a different alignment of flow directors. With respect to this latter option, a  
30 first 96-well embodiment might have its array of flow directors offset to align with a first quadrant of wells of a 384-well plate, while second, third and fourth embodiments would have similar arrays of flow directors on their lower surface each offset to allow

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facile alignment to a particular quadrant of wells of the 384-well plate.

Note that this invention does not require the use of either a 96-well plate or a 384-well plate. Preferably, however, the first well plate has x number of wells of a certain volume and the second well plate has y number of wells of a different volume, with the well volume of the first well plate being greater than that of the second well plate and with the number of wells in the second well plate being greater than that of the first well plate. More specifically, the number of wells in the second well plate is preferably a multiple of the number of wells in the first plate. Thus, the second well plate can be employed to receive samples from two or more first well plates. This capability further enhances the transfer, filtration and purification processes in accordance with the present invention. Thus, those skilled in the art will understand that the 96-well plate and 384-well plate are discussed herein by way of specific example only and other multiwell plates can be employed without departing from the scope of the present invention as defined by the claims appended herewith.

Since in this example three out of four wells will comprise open wells (i.e., be unused) during the stacking of one 96-well filter plate atop a 384-well plate, these open wells could become dry during the transfer process if they include a separation or purification media. Further, these wells could be subject to cross-contamination from material being transferred to the selected quadrant of wells of the 384-well plate. In order to prevent this, a stack

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assembly in accordance with this invention has a mechanism for sealing the non-used or open wells of the 384-well plate 20 during the transfer of material from the 96-well plate 10 to the 384-well plate. As one embodiment, gasket 30 (Fig. 2) is affixed to the bottom surface 18 of each 96-well plate 10 having material to be transferred to the 384-well plate. Gasket 30 fills the space between drip directors 16 depending from the 96-well plate. Thus, when the 96-well plate is aligned over a respective set of wells of the 384-well plate, gasket 30 will automatically cover open wells of the 384-well plate to prevent cross-contamination of the wells during transfer of material to the selected well set and/or to prevent the drawing of air through the open wells when a vacuum is applied to the outlets of the 384-well plate, thereby preventing drying of the wells. The gasket may be fabricated, for example, of a closed-cell foam material or rubber.

In accordance with the present invention, Figs. 8 & 9 depict partial cross-sectional views of a first 96-well plate 10 and a second 96-well plate 10', respectively, disposed over different sets of wells 23 & 23' in a 384-well plate 20. As shown, drip directors 16 register with and depend into corresponding wells 23,23' in the 384-well plate 20 when the 96-well plates 10,10' are stacked atop the 384-well plate. Gaskets 30 affixed, for example, to the lower surface of each 96-well plate 10,10', serve to seal the open wells 23 or 23' in the 384-well plate during transfer of material from the respective wells 13 of the 96-well plates 10,10' as described above.

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An alternate embodiment of a sealing mechanism pursuant to this invention is depicted in Figs. 10 & 11. This approach comprises an O-ring or rim gasket 50, which may be disposed atop the 384-well plate as shown, or conceivably could comprise a separate structure from the 384-well plate. If comprising a separate structure, gasket 50 would be stacked as shown atop the 384-well plate prior to placement of a 96-well plate thereon for transfer of fluid between plates. Gasket 50 operates to seal the ambient atmosphere from the interior region between the 96-well plate (not shown) and the 384-well plate so that when a vacuum is applied to outlets 26 of the 384-well plate, air will not be drawn through open wells of the plate and cause drying of the wells.

As an enhancement, the 384-well plate could be fitted with a flexible, puncturable membrane 52 so that when the flow directors of a 96-well plate are placed in registration with a corresponding set of wells 23,23' of the 384-well plate, the flow directors will puncture membrane 52 to allow transfer of material from the 96-well plate to the 384-well plate, with the balance of membrane 52 operating as a gasket which covers the openings to the unselected wells.

As a variation or further option, the amount of air passing through the open wells in the 384-well plate may be further reduced by providing a wetted porous material such as a membrane or frit 60 atop, for example, a purification media 62 packed in each well 23 as shown in Fig. 12. Media 62 is disposed over an additional frit 64 placed in the bottom end of each well. Frit or membrane 60 is assumed to have

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a pore size fine enough so that when wetted it does not allow air to easily pass through. For example, pore sizes for frit 60 could be between 0.1  $\mu\text{m}$  and 10  $\mu\text{m}$ . As a further advantage to this enhancement, provision of a porous material such as a frit or membrane on top of the purification media within the wells of the 384-well plate also serves to distribute more evenly by capillary action any reagent added, such as an elution buffer. This is particularly noticeable when a relatively small volume of buffer is used.

Fig. 13 depicts a still further enhancement wherein sealing between the outlets or drip directors 16 (Fig. 2) of the 96-well plate and corresponding wells of a quadrant of the 384-well plate can be achieved by configuring each drip director 16' to tightly mesh with an inlet 23' of a corresponding well of the 384-well plate when the 96-well plate is placed atop the 384-well plate. By so configuring each outlet 16' of the top plate and inlet of the receiving plate, an improved seal between the wells of the 96-well plate and the 384-well plate is achieved to prevent cross-contamination of wells during transfer of material from the 96-well plate to the 384-well plate.

As noted above, transfer of material from the 96-well plate to the 384-well plate is facilitated by the application of a vacuum at outlets 26 of the 384-well plate 20. Fig. 14 depicts a top plan view of a vacuum manifold configured and sized to receive the lower surface of the 384-well plate, while Fig. 15 depicts a cross-sectional view of a multiplate stack in accordance with the present invention disposed

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atop vacuum manifold 70 of Fig. 14. Manifold 70 is designed to readily seal to the lower surface of the 384-well plate when the stack is disposed thereon. For example, a gasket 72 could be provided along an appropriately sized shelf in manifold 70. Liquid transferred from the 96-well plate into and through the 384-well plate can be removed into a collection well 74 in manifold 70.

Also as noted above, alignment of the first multiwell plate atop the second multiwell plate can be facilitated by incorporating an alignment guide on either the first plate or the second plate. Figs. 16 & 17 depict different implementations of an alignment guide affixed to a 96-well plate 100 such that the 96-well plate registers with a different quadrant of wells in a 384-well plate 200. In Fig. 16, the alignment guide is secured to a first corner of the 96-well plate so that a multiwell stack 400 is produced wherein the flow directors of the 96-well plate 100 automatically align to a first set of wells in the 384-well plate 200, and in Fig. 17 the alignment guide is affixed to a different corner of the 96-well plate 100 so that a different alignment within the multiwell stack 400' is automatically produced when the 96-well plate is placed atop the 384-well plate. Those skilled in the art will understand that automatic alignment to one quadrant of the remaining quadrants of wells in the 384-well plate can be achieved by affixing an appropriate alignment guide to one of the remaining corners of the 96-well plate. As a variation on the embodiments of Figs. 16 & 17, the alignment guides depicted could alternatively be secured to different corners of the 384-well plates such that the 96-well plate could

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only register with a desired set of wells of the 384-well plates when stacked atop the 384-well plate with a side surface in contact with the alignment guide.

**Figs. 18a-22** depict certain additional enhancements to a multiwell multiplate stack and method for processing biological/chemical samples using the same in accordance with the principles of the present invention. Significant concerns in transferring samples from a first multiwell plate to a second multiwell plate as proposed herein include: (1) insuring consistent and proper alignment of the first multiwell plate over the second multiwell plate; and (2) detecting any cross-talk or cross-contamination of samples from different wells of one or more transferring multiwell plates into one or more wells of the receiving multiwell plate. For purposes of discussion, **Figs. 18a-22** assume that the first (or transferring) multiwell plate comprises a 96-well plate and the second (or receiving) multiwell plate comprises a 384-well plate. However, those skilled in the art will understand that either or both of these well plates may contain a different number of wells arranged in any regular array. Further, note that **Figs. 18a-21c** depict the wells of the first multiwell plate as being cylindrical in shape. Alternatively, the square or rectangular-shaped wells of **Figs. 1-17** could be employed.

As an enhancement to the alignment guides depicted in **Figs. 16 & 17**, color-coding of each alignment guide on the 96-well plates 100a, 100b, 100c and 100d of **Figs. 18a, 19a, 20a and 21a**, and color-coding of the appropriate corner of the 384-well plate 200 with a matching color can be

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advantageously employed in accordance with the present invention. With color-coding of the alignment guides on the 96-well plates and the corners of the 384-well plate, a user can quickly and easily align each 96-well plate to the 384-well plate and thus the wells of the 96-well plate to the desired quadrant of wells in the 384-well plate without having to track where they are in the aligning sequence. In another embodiment, each of the 96-well plates themselves may be color-coded to match the color of a particular corner of the receiving plate.

By way of example, Figs. 18a-18c depict a 96-well plate 100a having a red-coded alignment guide, Figs. 19a-19c depict a 96-well plate 100b having a green-coded alignment guide, Figs. 20a-20c depict a 96-well plate 100c having a blue-coded alignment guide and Figs. 21a-21c depict a 96-well plate 100d having a yellow-coded alignment guide. Correspondingly, the 384-well plate 200 of Figs. 18c, 19c, 20c and 21c has matching color-coding at each one of the four corners of the 384-well plate. Note that in this example, it is assumed that the shape and size of each 96-well plate and the 384-well plate are similar.

Note also that the colors red, yellow, green and blue are provided for example only and that the claims presented herewith are not limited to any specific color selection. Further, those skilled in the art will note that other alignment indicia besides color could be employed. For example, various positional symbols could be used in association with each 96-well plate and its alignment



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guide for aligning to corresponding symbols on the 384-well plate. Also, the alignment indicia (although preferably associated with the alignment guide and a corresponding corner of the 384-well plate) could be disposed remotely from the alignment guide and the corresponding corner of the 384-well plate. In addition, the alignment mechanism proposed herein, including the alignment guide and alignment indicia, may be used independent of or in combination with a sealing mechanism as described hereinabove, such as gasket 30 of Fig. 2.

In order for a user to readily determine whether cross-talk has occurred during the various transfer steps, a transfer indicia, such as color-coding of the samples, is used to track transfer of samples from each of the 96-well plates to the 384-well plate. Specifically, the filters 12a, 12b, 12c and 12d in the wells of the 96-well plates of Figs. 18a, 19a, 20a and 21a can be pre-loaded with a non-toxic, inert colorant, such as food coloring marketed by McCormick's of Hunt Valley, Maryland. In one embodiment, the 96-well plates comprise filter plates and the pre-loaded colorant is allowed to dry on the filters before introduction of the samples into the 96-well plates. When the 96-well plates are used in a transfer process as described hereinabove, all samples from a particular 96-well plate will be a common color. If there is any deviation from the expected color in a well of the 384-well plate or the color appears in a well outside the subset of wells intended to receive samples from the particular 96-well plate, cross-talk has occurred. In many processes, the presence of food coloring will not interfere with the downstream processing steps

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performed on the samples, DNA purification processing being one example. As noted, **Figs. 18a, 19a, 20a and 21a** respectively depict color-coded filters within the wells of the four 96-well plates. Each of these  
5 96-well plates employs filters with a common, unique color code, and in the embodiment shown, the color coding of the filters matches the color coding of the alignment indicia of the alignment guides. However, this is not a requirement. Also, as an alternative,  
10 the color of the entire 96-well plate could match the color coding of the filters contained therein. Further, in certain processes, only a selected well or wells of the 96-well plate may contain a color-coded filter in accordance with this aspect of the  
15 present invention.

As a specific implementation, using a multi-channel pipette, 10  $\mu$ l of red colored solution (comprising, e.g., one drop of food coloring to 30 ml of distilled water) is loaded onto the filters of  
20 each well of a 96-well plate, and allowed to dry. This process is repeated with three other 96-well plates using yellow, green and blue solutions to produce the colored filters shown in **Figs. 18a, 19a, 20a and 21a**. Samples are then loaded into the wells  
25 of the 96-well plates. In accordance with the principles of this invention, these samples are subsequently transferred to a second well plate, for example, a 384-well plate, stepwise. Beginning with the red colored plate, all of the samples transferred  
30 from the red plate should be red, and the other wells of the 384-well plate should remain original color. The process is repeated with the yellow plate, and if any cross-talk occurs within the 384-well plate with the previously transferred red samples or the wells

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expected to be empty, the sample color would change or the wells expected to be empty would turn yellow. Similarly, samples from the green plate are transferred and then the blue plate. Using this

5 method, at any time during the transfer process, the user can readily ascertain whether any cross-talk has occurred simply by looking at the colors, e.g., of the filter and/or media in the wells of the 384-well

10 plate to determine if there is any deviation from a predetermined color pattern. Fig. 22 depicts one example of a predetermined color pattern for the 384-well plate assuming proper transfer of colored

samples from four 96-well plates as described herein.

Note that the amount of colored solution

15 employed is not critical, but in general should be between 2  $\mu$ l to 30  $\mu$ l, with 5  $\mu$ l to 15  $\mu$ l being preferred for the 96-well plates described. The colored solution can be added using various means, including a dropper, single pipette, multi-channel

20 pipette, and automated means such as a multi-dropper machine marketed by Labsystems OY, of Helsinki, Finland. Further, although red, yellow, green and blue are preferred colors for both the alignment color coding and transfer color coding systems in

25 accordance with this invention, any variation of these colors may be used, and the intensity of color of each solution can be varied by using different amounts of colorant in the stock solutions. In addition, the sequence in which the samples are

30 transferred from the differently dyed plates can be varied, but again, the sequence of red, yellow, green and blue may be preferred. As an alternative sequence, yellow, green, blue and red may be employed. Moreover, while it is more efficient to

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dye the filters of all wells in a plate, one could alternatively dye only filters of a selected well or wells which will actually be used.

The color-coded alignment technique and color-coded sample contamination detection technique described herein can be used independently or in combination. In a preferred embodiment, the color of the alignment means and the dyed filter of a 96-well plate will be the same. Further, the 96-well plate can be manufactured and marketed with the colorant pre-loaded on the filters of the 96-well filter plate and/or with the color-coded alignment guides already mounted on the plates. These plates could be available individually, or in pre-packaged kits. For example, a kit might comprise four 96-well plates, one each with a unique color-coded (e.g., red, yellow, green and blue) alignment guide, and optionally, filters pre-loaded with the corresponding colored dye. The kit optionally includes a 384-well plate having the corners color coded to match the coloring of the alignment means on the four 96-well plates.

In accordance with the present invention, various kits containing different multiwell plates to be stacked can be assembled. In most embodiments, these kits have at least two different types of multiwell plates which allow for direct transfer of material as described hereinabove.

For example, a kit for culturing and purifying a product or biological molecules of interest, such as a plasmid, can be provided wherein the kit comprises one to four 96-well filter plates for culture and

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subsequent clarification of lysed/potassium acetate precipitated product (such as a plasmid) and one or more 384-well plates having a porous retaining material, such as a filter or membrane, disposed in the bottom of each well. The kit would also include a gasket (such as gasket 30) affixed to the bottom of each 96-well plate or one or more rim gaskets for sealing the perimeter of the space between a 96-well plate and a 384-well plate when the 96-well plate is stacked thereon. Such kits may optionally include one or both of the (a) color-coded alignment guides, and (b) the color-coded contamination detection means previously described herein.

The 96/384 kits of the present invention further comprise reagents for culturing and purifying biological molecules, wherein the reagents can comprise a resuspension buffer, a lysis buffer, a potassium acetate ("KAc") precipitation buffer, and an elution buffer.

As a further example, a kit in accordance with the present invention would again comprise a kit for culturing and purifying a desired product or biological molecules of interest, such as a plasmid. This kit would include one 96-well filter plate for culturing and subsequent clarification of lysed/potassium acetate precipitated product, such as a plasmid, and one 96-well plate having a porous retaining material disposed in the bottom of each well. Each well of the second 96-well multiwell plate would be packed with a volume of size exclusion media on top of the porous retaining material and a volume of an absorptive media packed on top of the size exclusion media. A 96-well receiving plate is

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also included. Thus, use of this kit would involve transfer of material directly between 96-well plates.

The 96-well kits of the present invention may further comprise reagents for culturing and purifying biological molecules. The reagents could comprise a resuspension buffer, a lysis buffer, a potassium acetate ("KAc") precipitation buffer, a wash buffer, a desalting buffer or an elution buffer.

The various reagents may be loaded into the wells of the 96-well or 384-well plates using a commercially available 96-well or 384-well pipettor, or by automated means such as a multi-dropper such as that sold by Labsystems OY of Helsinki, Finland. The 96-well pipettor may be used with either the 96-well or 384-well plates. In one embodiment of the present invention, the wells of a 384-well plate are prefilled with 100  $\mu$ l of washing buffer (e.g., 0.5 M NaCl, 50 mM Tris), and this wash plate is placed above a 384-well plate containing the absorptive media, and the wash buffer is drawn through the absorptive media plate by a vacuum. Various other examples will be evident to those skilled in the art based upon the information provided herein.

To repeat, those skilled in the art will note from the above discussion that various techniques are provided herein for directly transferring samples from a first well plate having a first number of wells to a second well plate having a second number of wells, wherein the second number of wells may be greater than the first number of wells. Preferably, the second number of wells is a multiple of the first number of wells. As a specific example discussed

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herein, the first well plate may comprise a 96-well plate and the second well plate a 384-well plate. Significant time and processing complexity is saved by being able to directly transfer between two  
5 different multiwell plates. Pipetting apparatus is unnecessary to accomplish the transfer.

In addition to direct transfer of samples between well plates, a technique is provided herein to prevent cross-contamination between wells of the  
10 receiving plate, as well as to prevent drying of open wells within the receiving plate. In accordance with the principles of this invention, the first well plate may comprise a filter plate so that simultaneous transfer and filtering of samples occurs  
15 during the movement of samples from the first well plate to the second well plate. Further, the second well plate can comprise a chromatographic media so that purification of the sample can also simultaneously occur with transfer of the sample from  
20 the first well plate into and through the second well plate. Thus, in accordance with the principles of this invention, a greater volume of sample in the first well plate than can be accommodated in the second well plate can be simultaneously filtered in  
25 the first well plate, transferred from the first well plate to the second well plate and purified in the second well plate, before being discharged.

While the invention has been described in detail herein in accordance with certain preferred  
30 embodiments thereof, many modifications and changes therein may be effected by those skilled in the art. For example, those skilled in the art will understand that the concepts presented herein can be used in a

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multitude of combinations. Accordingly, it is intended by the appended claims to cover all such modifications and changes as fall within the true spirit and scope of the invention.



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Claims

1           1.    A device for processing biological/chemical  
2    samples comprising:

3                   a first multiwell plate having x wells  
4           arranged in a regular array, each well of said x  
5           wells being capable of receiving a separate  
6           sample, and wherein each well of said x wells  
7           has an outlet at a lower surface of the first  
8           multiwell plate;

9                   a second multiwell plate having y wells  
10          arranged in a regular array, each well of said y  
11          wells being capable of receiving a separate  
12          sample, and wherein  $y > x$  and said outlets at  
13          the lower surface of said first multiwell plate  
14          are arranged to register with corresponding  
15          inlets of x' wells of said y wells of said second  
16          multiwell plate when said first multiwell plate  
17          is stacked atop said second multiwell plate,  
18          wherein  $x' = x$ ; and

19                   means for sealing said first multiwell  
20          plate to said second multiwell plate when said  
21          first multiwell plate is stacked atop said  
22          second multiwell plate so that samples can be  
23          transferred from said x wells of said first  
24          multiwell plate to said x' wells of said second  
25          multiwell plate without cross-contamination  
26          occurring between wells of said second multiwell  
27          plate.

1           2.    The device of claim 1, wherein said first  
2    multiwell plate comprises a filter plate which

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3 filters samples in said x wells simultaneous with  
4 transfer of samples from said filter plate to said  
5 second multiwell plate.

1 3. The device of claim 2, wherein said second  
2 multiwell plate comprises a purification plate for  
3 separating components of samples transferred from  
4 said filter plate to said purification plate.

1 4. The device of claim 2, wherein  $y = (x \times n)$ ,  
2 wherein  $n \geq 2$ .

1 5. The device of claim 1, wherein said x wells  
2 of said first multiwell plate are of greater volume  
3 than said x' wells of said second multiwell plate, and  
4 wherein said device further comprises means for  
5 drawing samples from said first multiwell plate into  
6 and through said second multiwell plate.

1 6. The device of claim 5, wherein each of said  
2 x' wells of said second multiwell plate has an outlet  
3 at a lower surface of said second multiwell plate,  
4 and said means for drawing samples from said first  
5 multiwell plate to said second multiwell plate  
6 comprises a vacuum apparatus, said vacuum apparatus  
7 including a vacuum manifold configured to seal  
8 against the lower surface of said second multiwell  
9 plate, wherein samples within said first multiwell  
10 plate are drawn into and through said second  
11 multiwell plate by said vacuum apparatus.

1 7. The device of claim 6, wherein said first  
2 multiwell plate comprises a filter plate and said  
3 second multiwell plate comprises a purification  
4 plate.

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1           8.    The device of claim 7, wherein said x wells  
2   of said first multiwell plate comprise 96 wells and  
3   wherein said y wells of said second multiwell plate  
4   comprise an integer multiple of said 96 wells.

1           9.    The device of claim 8, wherein said y wells  
2   of said second multiwell plate comprise 384 wells or  
3   864 wells.

1           10.   The device of claim 6, wherein each well of  
2   said y wells of said second multiwell plate contains  
3   a frit or membrane having a pore size fine enough so  
4   that when wetted air is inhibited from passing  
5   therethrough.

1           11.   The device of claim 5, wherein each well of  
2   said first multiwell plate can hold approximately 400  
3    $\mu$ l, and wherein each well of said second multiwell  
4   plate can hold approximately 120  $\mu$ l.

1           12.   The device of claim 1, wherein said means  
2   for sealing comprises a gasket affixed to a lower  
3   surface of said first multiwell plate, said gasket  
4   sealing all open wells of the second multiwell plate  
5   when said first multiwell plate is stacked atop said  
6   second multiwell plate, said open wells comprising  
7   wells of said y wells other than said x' wells  
8   receiving samples from said first multiwell plate.

1           13.   The device of claim 1, wherein said means  
2   for sealing comprises an O-ring disposed between said  
3   first multiwell plate and said second multiwell plate  
4   when the first multiwell plate is stacked atop the  
5   second multiwell plate, said O-ring forming an air  
6   seal to prevent air from being drawn into open wells

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7 of said second multiwell plate, said open wells  
8 comprising wells of said y wells other than said x'  
9 wells receiving samples from said first multiwell  
10 plate.

1 14. The device of claim 13, further comprising  
2 a puncturable film disposed across an upper surface  
3 of said second multiwell plate, and wherein said  
4 outlets of said x wells of said first multiwell plate  
5 comprise drip directors, said drip directors  
6 comprising means for puncturing said puncturable film  
7 upon stacking of said first multiwell plate atop said  
8 second multiwell plate, said puncturable film sealing  
9 open wells of said second multiwell plate.

1 15. The device of claim 1, further comprising  
2 means for automatically aligning said x wells of said  
3 first multiwell plate to said x' wells of said second  
4 multiwell plate when said first multiwell plate is  
5 stacked atop said second multiwell plate.

1 16. The device of claim 15, wherein said means  
2 for automatically aligning comprises an alignment  
3 guide coupled to either said first multiwell plate or  
4 said second multiwell plate such that said x wells of  
5 said first multiwell plate automatically align to  
6 said x' wells of said second multiwell plate when  
7 said first multiwell plate is stacked atop said  
8 second multiwell plate.

1 17. The device of claim 16, wherein said  
2 alignment guide is affixed to a corner of said first  
3 multiwell plate.

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1           18. A method for processing biological/chemical  
2    samples comprising:

3           (a) providing a first multiwell plate  
4    having x wells arranged in a regular array, each  
5    well of said x wells having an outlet at a lower  
6    surface of said first multiwell plate, and  
7    wherein each well of said x wells receives a  
8    sample;

9           (b) providing a second multiwell plate  
10   having y wells arranged in a regular array, each  
11   well of said y wells being capable of receiving  
12   a sample, and wherein  $y > x$  and said outlets at  
13   the lower surface of the first multiwell plate  
14   are arrayed to register with corresponding  
15   inlets of x' wells of said second multiwell plate  
16   when said first multiwell plate is stacked atop  
17   said second multiwell plate, wherein  $x' = x$ ;

18           (c) stacking said first multiwell plate  
19   atop said second multiwell plate with said  
20   outlets of said x wells of said first multiwell  
21   plate registering with said corresponding inlets  
22   of said x' wells of said second multiwell plate;  
23   and

24           (d) subsequent to said stacking (c),  
25   transferring samples from said x wells of said  
26   first multiwell plate to said x' wells of said  
27   second multiwell plate through said outlets of  
28   said x wells of said first multiwell plate.

1           19. The method of claim 18, wherein each of  
2    said x' wells of said second multiwell plate has an

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3 outlet at a lower surface of said second multiwell  
4 plate, and wherein said transferring comprises  
5 applying a vacuum to said outlets of said second  
6 multiwell plate to draw samples from said first  
7 multiwell plate into and through said second  
8 multiwell plate.

1 20. The method of claim 19, wherein said first  
2 multiwell plate comprises a filter plate, and said  
3 method further comprises simultaneous with said  
4 transferring (d), filtering said samples within said  
5 x wells of said filter plate.

1 21. The method of claim 20, wherein said second  
2 multiwell plate comprises a purification plate, and  
3 said transferring comprises purifying said samples  
4 transferred into said x wells of said purification  
5 plate simultaneous with said samples being drawn  
6 therethrough.

1 22. The method of claim 18, wherein  $y = (x \times n)$   
2 and  $n \geq 2$ , and wherein said method further comprises:

3 (i) removing said first multiwell plate  
4 from atop said second multiwell plate after  
5 transferring said samples from said first  
6 multiwell plate to said second multiwell plate;

7 (ii) providing a third multiwell plate  
8 having x wells arranged in a regular array, each  
9 well of said x wells having an outlet at a lower  
10 surface of said third multiwell plate, and  
11 wherein each well of said x wells contains a  
12 sample;

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13           (iii) wherein said outlets at the lower  
14 surface of said third multiwell plate are each  
15 arranged to register with corresponding inlets  
16 of x" wells of said second multiwell plate when  
17 said third multiwell plate is stacked atop said  
18 second multiwell plate, wherein x"=x and said x"  
19 wells comprise a different subset of wells than  
20 said x' wells of said second multiwell plate;

21           (iv) stacking said third multiwell plate  
22 atop said second multiwell plate with said  
23 outlets of said x wells of said third multiwell  
24 plate registering with said corresponding inlets  
25 of said x" wells of said second multiwell plate;  
26 and

27           (v) subsequent to said stacking of said  
28 third multiwell plate atop said second multiwell  
29 plate, transferring samples from said x wells of  
30 said third multiwell plate to said x" wells of  
31 said second multiwell plate through said outlets  
32 of said x wells of said third multiwell plate.

1       23. The method of claim 22, wherein said  
2 transferring (v) comprises applying a vacuum to said  
3 stack of said third multiwell plate atop said second  
4 multiwell plate to draw samples from said third  
5 multiwell plate into said x" wells of said second  
6 multiwell plate.

1       24. The method of claim 23, wherein said third  
2 multiwell plate comprises a filter plate, and said  
3 transferring comprises simultaneously filtering said  
4 samples in said x wells of said third multiwell plate

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5 during transfer of said samples to said second  
6 multiwell plate.

1 25. The method of claim 18, further comprising  
2 creating a seal between the lower surface of said  
3 first multiwell plate and an upper surface of said  
4 second multiwell plate upon said stacking of said  
5 first multiwell plate atop said second multiwell  
6 plate, said seal preventing cross-contamination  
7 between wells of said second multiwell plate during  
8 said transferring of samples from said first  
9 multiwell plate to said second multiwell plate.

1 26. The method of claim 25, wherein said  
2 creating of said seal comprises providing said first  
3 multiwell plate with a gasket on said lower surface,  
4 said gasket sealing all open wells of said second  
5 multiwell plate upon said stacking of said first  
6 multiwell plate atop said second multiwell plate,  
7 said open wells comprising wells of said y wells  
8 other than said x' wells receiving samples during said  
9 transferring (d).

1 27. The method of claim 18, wherein said  
2 providing (a) comprises providing said first  
3 multiwell plate with x wells each capable of holding  
4 400  $\mu$ l of sample, and wherein said providing (b)  
5 comprises providing said second multiwell plate with  
6 y wells each capable of holding approximately 120  $\mu$ l  
7 of sample, said first multiwell plate comprising a  
8 96-well plate and said second multiwell plate  
9 comprising a 384-well plate.

1 28. A multiwell plate having x wells arranged  
2 in a regular array, each well of said x wells being



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3 capable of receiving a separate sample, and wherein  
4 each well of said x wells has an outlet at a lower  
5 surface of said multiwell plate, said multiwell plate  
6 further comprising a gasket affixed to said lower  
7 surface of said multiwell plate, said gasket residing  
8 between said outlets of said x wells of said  
9 multiwell plate, wherein when said multiwell plate is  
10 stacked atop another multiwell plate having y wells,  
11 wherein  $y > x$ , said gasket seals open wells of said  
12 another multiwell plate from cross-contamination  
13 during transfer of samples from said x wells of said  
14 multiwell plate to said another multiwell plate, said  
15 open wells comprising wells of said another multiwell  
16 plate not registering with said outlets of said x  
17 wells of said multiwell plate when said multiwell  
18 plate is stacked atop said another multiwell plate.

1 29. A device for processing biological/chemical  
2 samples comprising:

3 a first multiwell plate having x wells  
4 arranged in a regular array, each well of said x  
5 wells being capable of receiving a separate  
6 sample, and wherein each well of said x wells  
7 has an outlet at a lower surface of the first  
8 multiwell plate;

9 a second multiwell plate having y wells  
10 arranged in a regular array, each well of said y  
11 wells being capable of receiving a separate  
12 sample, and wherein  $y \geq x$  and said outlets at  
13 the lower surface of said first multiwell plate  
14 are arranged to register with corresponding  
15 inlets of x' wells of said y wells of said  
16 second multiwell plate when said first multiwell

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17 plate is aligned with and stacked atop said  
18 second multiwell plate, wherein  $x'=x$ ; and

19 means for aligning said first multiwell  
20 plate to said second multiwell plate so that  
21 said  $x$  wells of said first multiwell plate  
22 automatically align to said  $x'$  wells of said  
23 second multiwell plate when said first multiwell  
24 plate is stacked atop said second multiwell  
25 plate using said means for aligning, whereby  
26 samples can be transferred from said  $x$  wells of  
27 said first multiwell plate to said  $x'$  wells of  
28 said second multiwell plate.

1 30. The device of claim 29, wherein said means  
2 for aligning comprises first alignment indicia on  
3 said first multiwell plate and corresponding second  
4 alignment indicia on said second multiwell plate,  
5 wherein aligning of said first alignment indicia and  
6 said second alignment indicia when stacking said  
7 first multiwell plate atop said second multiwell  
8 plate facilitates said automatic aligning of said  $x$   
9 wells of said first multiwell plate to said  $x'$  wells  
10 of said second multiwell plate.

1 31. The device of claim 30, wherein said first  
2 alignment indicia and said corresponding second  
3 alignment indicia comprise matching color indicia.

1 32. The device of claim 30, wherein  $y=(x \times n)$   
2 and  $n \geq 2$ , and wherein said device further comprises  
3  $n$  first multiwell plates each having  $x$  wells arranged  
4 in a regular array, and each of said  $x$  wells being  
5 capable of receiving a separate sample, and wherein  
6 said means for aligning comprises  $n$  first alignment

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7     indicia on said n first multiwell plates, each first  
8     alignment indicia being disposed on a separate first  
9     multiwell plate, said means for aligning further  
10    comprising at least two second alignment indicia on  
11    said second multiwell plate, wherein at least two  
12    first alignment indicia on said first multiwell  
13    plates have corresponding second alignment indicia on  
14    said second multiwell plate.

1           33. The device of claim 32, wherein  $n=4$ , and  
2     wherein said means for aligning comprises four first  
3     alignment indicia one each on said four first  
4     multiwell plates, and four corresponding second  
5     alignment indicia on said second multiwell plate,  
6     each first alignment indicia having a corresponding  
7     second alignment indicia on said second multiwell  
8     plate, and wherein each first alignment indicia and  
9     corresponding second alignment indicia comprise  
10    matching color indicia.

1           34. The device of claim 33, wherein said x  
2     wells of said first multiwell plates comprise 96-  
3     wells and wherein said y wells of said second  
4     multiwell plate comprise 384-wells.

1           35. The device of claim 30, wherein said means  
2     for aligning further comprises an alignment guide  
3     coupled to either said first multiwell plate or said  
4     second multiwell plate so that said x wells of said  
5     first multiwell plate automatically align to said x'  
6     wells of said second multiwell plate when said first  
7     multiwell plate is stacked atop said second multiwell  
8     plate using said alignment guide.

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1           36. The device of claim 35, wherein said  
2 alignment guide is coupled to said first multiwell  
3 plate and said first alignment indicia is disposed  
4 near said alignment guide.

1           37. The device of claim 36, wherein said first  
2 multiwell plate and said second multiwell plate have  
3 a common shape and similar size, and wherein said  
4 alignment guide is disposed at a corner of said first  
5 multiwell plate and extends downward therefrom for  
6 aligning thereof to a corner of said second multiwell  
7 plate, said corner of said second multiwell plate  
8 containing said corresponding second alignment  
9 indicia.

1           38. The device of claim 37, wherein said first  
2 multiwell plate and said second multiwell plate have  
3 a common rectangular shape, and wherein said x wells  
4 of said first multiwell plate comprise 96-wells, said  
5 y wells of said second multiwell plate comprise 384-  
6 wells, and said means for aligning comprises multiple  
7 second alignment indicia on said second multiwell  
8 plate, each second alignment indicia being disposed  
9 at a different corner of said second multiwell plate.

1           39. The device of claim 38, further comprising  
2 four first multiwell plates each having x wells  
3 arranged in a regular array, each well of said x  
4 wells being capable of receiving a separate sample,  
5 and wherein each well of said x wells has an outlet  
6 at a lower surface of the first multiwell plate, and  
7 wherein each multiwell plate of said four first  
8 multiwell plates has said common shape and similar  
9 size, and wherein said means for aligning comprises  
10 four alignment guides, each alignment guide being

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11 coupled to a different first multiwell plate so that  
12 said x wells of each first multiwell plate align to a  
13 different quadrant of said 384-wells of said second  
14 multiwell plate.

1 40. The device of claim 39, wherein said means  
2 for aligning further comprises four first alignment  
3 indicia on said four first multiwell plates, each  
4 first alignment indicia being disposed near the  
5 alignment guide coupled to a different first  
6 multiwell plate, and four second alignment indicia on  
7 said second multiwell plate, each first alignment  
8 indicia having a corresponding second alignment  
9 indicia on said second multiwell plate for  
10 facilitating aligning of each first multiwell plate  
11 to said second multiwell plate.

1 41. The device of claim 29, further comprising  
2 means for sealing said first multiwell plate to said  
3 second multiwell plate so that said first multiwell  
4 plate is stacked atop said second multiwell plate so  
5 that samples can be transferred from said x wells of  
6 said first multiwell plate to said x' wells of said  
7 second multiwell plate without cross-contamination  
8 occurring between wells of said second multiwell  
9 plate.

1 42. A device for processing biological/chemical  
2 samples comprising:

3 a first multiwell plate having x wells  
4 arranged in a regular array, each well of said x  
5 wells being capable of receiving a separate  
6 sample;

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7           a second multiwell plate having y wells  
8           arranged in a regular array, each well of said y  
9           wells being capable of receiving a separate  
10          sample; and

11           transfer indicia for indicating transfer of  
12          sample from said first multiwell plate to said  
13          second multiwell plate, said transfer indicia  
14          being disposed within said first multiwell plate  
15          and transferring from said first multiwell plate  
16          to said second multiwell plate with transfer of  
17          sample therebetween.

1           43. The device of claim 42, wherein said  
2          transfer indicia comprises color indicia.

1           44. The device of claim 42, wherein each well  
2          of said x wells of said first multiwell plate has an  
3          outlet at a lower surface of the first multiwell  
4          plate, and wherein  $y \geq x$  and said outlets at the  
5          lower surface of said first multiwell plate are  
6          arranged to register with corresponding inlets of x'  
7          wells of said y wells of said second multiwell plate  
8          when said first multiwell plate is stacked atop said  
9          second multiwell plate, wherein  $x' = x$ , and wherein  
10         said transfer indicia comprises means for tracking  
11         transfer of samples from wells of said first  
12         multiwell plate to wells of said second multiwell  
13         plate, and simultaneously for indicating whether  
14         cross-contamination has occurred between wells of  
15         said second multiwell plate.

1           45. The device of claim 44, wherein said  
2          transfer indicia comprises inert color indicia  
3          disposed within at least one well of said first

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4 multiwell plate, said inert color indicia  
5 transferring from said at least one well of said  
6 first multiwell plate to at least one well of said  
7 second multiwell plate with transfer of samples from  
8 said first multiwell plate to said second multiwell  
9 plate.

1 46. The device of claim 45, wherein  $y=(x \times n)$ ,  
2  $n \geq 2$ , and wherein said device further comprises  $n$   
3 first multiwell plates each having  $x$  wells arranged  
4 in a regular array, and each of said  $x$  wells is  
5 capable of receiving a separate sample, and wherein  
6 said  $x$  wells of each first multiwell plate contain a  
7 unique color indicia, said unique color indicia of  
8 each first multiwell plate being inert and being  
9 transferred from said  $x$  wells of said first multiwell  
10 plate to corresponding  $x'$  wells of said second  
11 multiwell plate upon transfer of samples from said  
12 first multiwell plate to said second multiwell plate.

1 47. The device of claim 46, wherein  $n=4$ , and  
2 wherein said four first multiwell plates comprise  
3 four unique color indicia, said four unique color  
4 indicia comprising red indicia, yellow indicia, green  
5 indicia, and blue indicia, each unique color indicia  
6 being inert and being contained within a different  
7 first multiwell plate, each first multiwell plate of  
8 said four first multiwell plates transferring samples  
9 to a different quadrant of wells of said  $y$  wells of  
10 said second multiwell plate, wherein said red,  
11 yellow, green and blue indicia are respectively  
12 transferred from said four first multiwell plates to  
13 said second multiwell plate with transfer of sample  
14 therebetween.

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1           48. The device of claim 44, further comprising  
2 means for aligning said first multiwell plate to said  
3 second multiwell plate so that said x wells of said  
4 first multiwell plate automatically align to said x'  
5 wells of said second multiwell plate when said first  
6 multiwell plate is stacked atop said second multiwell  
7 plate using said means for aligning.

1           49. The device of claim 48, wherein said means  
2 for aligning comprises first alignment indicia on  
3 said first multiwell plate and corresponding second  
4 alignment indicia on said second multiwell plate,  
5 wherein aligning of said first alignment indicia and  
6 said second alignment indicia when stacking said  
7 first multiwell plate atop said second multiwell  
8 plate facilitates said automatic aligning of said x  
9 wells of said first multiwell plate to said x' wells  
10 of said second multiwell plate.

1           50. The device of claim 49, wherein said first  
2 alignment indicia and said corresponding second  
3 alignment indicia comprise matching color indicia.

1           51. The device of claim 50, wherein said x  
2 wells of said first multiwell plate comprise 96-wells  
3 and said y wells of said second multiwell plate  
4 comprise 384-wells.

1           52. The device of claim 49, wherein said means  
2 for aligning further comprises an alignment guide  
3 coupled to either said first multiwell plate or said  
4 second multiwell plate so that said x wells of said  
5 first multiwell plate automatically align to said x'  
6 wells of said second multiwell plate when said first



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7 multiwell plate is stacked atop said second multiwell  
8 plate using said alignment guide.

1 53. The device of claim 52, wherein said  
2 alignment guide is coupled to said first multiwell  
3 plate and said first alignment indicia is disposed  
4 near said alignment guide.

1 54. The device of claim 53, wherein said first  
2 multiwell plate and said second multiwell plate have  
3 a common shape and similar size, and wherein said  
4 alignment guide is disposed at a corner of said first  
5 multiwell plate and extends downward therefrom for  
6 aligning thereof to a corner of said second multiwell  
7 plate, said corner of said second multiwell plate  
8 containing said corresponding second alignment  
9 indicia.

1 55. The device of claim 54, wherein said first  
2 multiwell plate and said second multiwell plate have  
3 a common rectangular shape, and wherein said x wells  
4 of said first multiwell plate comprise 96-wells and  
5 said y wells of said second multiwell plate comprise  
6 384-wells, and said means for aligning comprises  
7 multiple second alignment indicia on said second  
8 multiwell plate, each of said second alignment  
9 indicia being disposed at a different corner of said  
10 second multiwell plate.

1 56. The device of claim 55, further comprising  
2 four first multiwell plates each having x wells  
3 arranged in a regular array, each well of said x  
4 wells being capable of receiving a separate sample,  
5 and wherein each well of said x wells has an outlet  
6 in a lower surface of the first multiwell plate, and

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7 wherein each multiwell plate of said four first  
8 multiwell plates has said common shape and similar  
9 size, and wherein said means for aligning comprises  
10 four alignment guides, each alignment guide being  
11 coupled to a different first multiwell plate so that  
12 said x wells of each first multiwell plate align to a  
13 different quadrant of said 384-wells of said second  
14 multiwell plate when the first multiwell plate is  
15 stacked atop said second multiwell plate using the  
16 alignment guide.

1 57. The device of claim 56, wherein said means  
2 for aligning further comprises four first alignment  
3 indicia on said four first multiwell plates, each  
4 first alignment indicia being disposed near a  
5 different alignment guide coupled to one of said four  
6 first multiwell plates, and four second alignment  
7 indicia on said second multiwell plate, each first  
8 alignment indicia having a corresponding second  
9 alignment indicia on said second multiwell plate for  
10 facilitating aligning of each first multiwell plate  
11 to said second multiwell plate.

1 58. The device of claim 57, wherein each first  
2 alignment indicia and corresponding second alignment  
3 indicia comprise matching color indicia.

1 59. The device of claim 44, further comprising  
2 means for sealing said first multiwell plate to said  
3 second multiwell plate when said first multiwell  
4 plate is stacked atop said second multiwell plate so  
5 that samples can be transferred from said x wells of  
6 said first multiwell plate to said x' wells of said  
7 second multiwell plate without cross-contamination

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8 occurring between wells of said second multiwell  
9 plate.

1 60. A method for processing biological/chemical  
2 samples comprising:

3 (a) providing a first multiwell plate  
4 having x wells arranged in a regular array, each  
5 well of said x wells being capable of receiving  
6 a separate sample;

7 (b) providing a second multiwell plate  
8 having y wells arranged in a regular array, each  
9 well of said y wells being capable of receiving  
10 a sample;

11 (c) providing inert transfer indicia  
12 within at least one well of said x wells of said  
13 first multiwell plate;

14 (d) transferring sample from said first  
15 multiwell plate to said second multiwell plate,  
16 said transferring including transferring said  
17 transfer indicia from said at least one well of  
18 said first multiwell plate to at least one well  
19 of said second multiwell plate, wherein said  
20 transfer indicia tracks transfer of sample from  
21 said at least one well of said first multiwell  
22 plate to said at least one well of said second  
23 multiwell plate, and occurrence of cross-  
24 contamination between wells of said second  
25 multiwell plate can be monitored using said  
26 transfer indicia.

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1           61. The method of claim 60, wherein said  
2 providing (a) includes providing said first multiwell  
3 plate so that each well of said x wells has a filter,  
4 and wherein said transfer indicia comprises color  
5 indicia and said providing (c) comprises providing  
6 liquid color indicia within said at least one well of  
7 said x wells of said first multiwell plate, allowing  
8 said liquid color indicia to dry on the filters of  
9 said at least one well of said x wells, and  
10 thereafter, introducing sample into wells of said x  
11 wells of said first multiwell plate.

1           62. The method of claim 61, wherein said  
2 providing (c) comprises providing transfer indicia  
3 within each well of said x wells of said first  
4 multiwell plate.

1           63. The method of claim 62, wherein said  
2 providing (a) comprises providing said first  
3 multiwell plate so that each well of said x wells has  
4 an outlet at a lower surface of said first multiwell  
5 plate, said providing (b) comprises providing said  
6 second multiwell plate with y wells so that  $y \geq x$ ,  
7 said outlets at the lower surface of the first  
8 multiwell plate being arrayed to register with  
9 corresponding inlets of x' wells of said second  
10 multiwell plate when said first multiwell plate is  
11 stacked atop said second multiwell plate, wherein  
12  $x' = x$ , and wherein said method further comprises  
13 stacking said first multiwell plate atop said second  
14 multiwell plate with said outlets of said x wells of  
15 said first multiwell plate registering with said  
16 corresponding inlets of said x' wells of said second  
17 multiwell plate, said stacking occurring prior to  
18 said transferring (d).

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1           64. The method of claim 63, wherein each of  
2       said x' wells of said second multiwell plate has an  
3       outlet at a lower surface of said second multiwell  
4       plate, and wherein said transferring (d) comprises  
5       applying a vacuum to said outlets of said second  
6       multiwell plate to draw samples from said first  
7       multiwell plate into and through said second  
8       multiwell plate.

1           65. The method of claim 64, wherein said second  
2       multiwell plate comprises a purification plate, and  
3       said transferring (d) comprises purifying said  
4       samples transferred into said x' wells of said  
5       purification plate simultaneous with said samples  
6       being drawn therethrough, wherein said color indicia  
7       transfers from said first multiwell plate into said  
8       second multiwell plate with transfer of sample  
9       therebetween.

1           66. The method of claim 63, wherein said first  
2       multiwell plate comprises a 96-well plate and said  
3       second multiwell plate comprises a 384-well plate,  
4       and wherein said providing (a) further comprises  
5       providing three additional 96-well plates, and said  
6       providing (c) comprises providing a unique color  
7       indicia for each 96-well plate so that said  
8       transferring (d) of sample from each 96-well plate  
9       includes simultaneous tracking of said unique color  
10      indicia associated therewith.

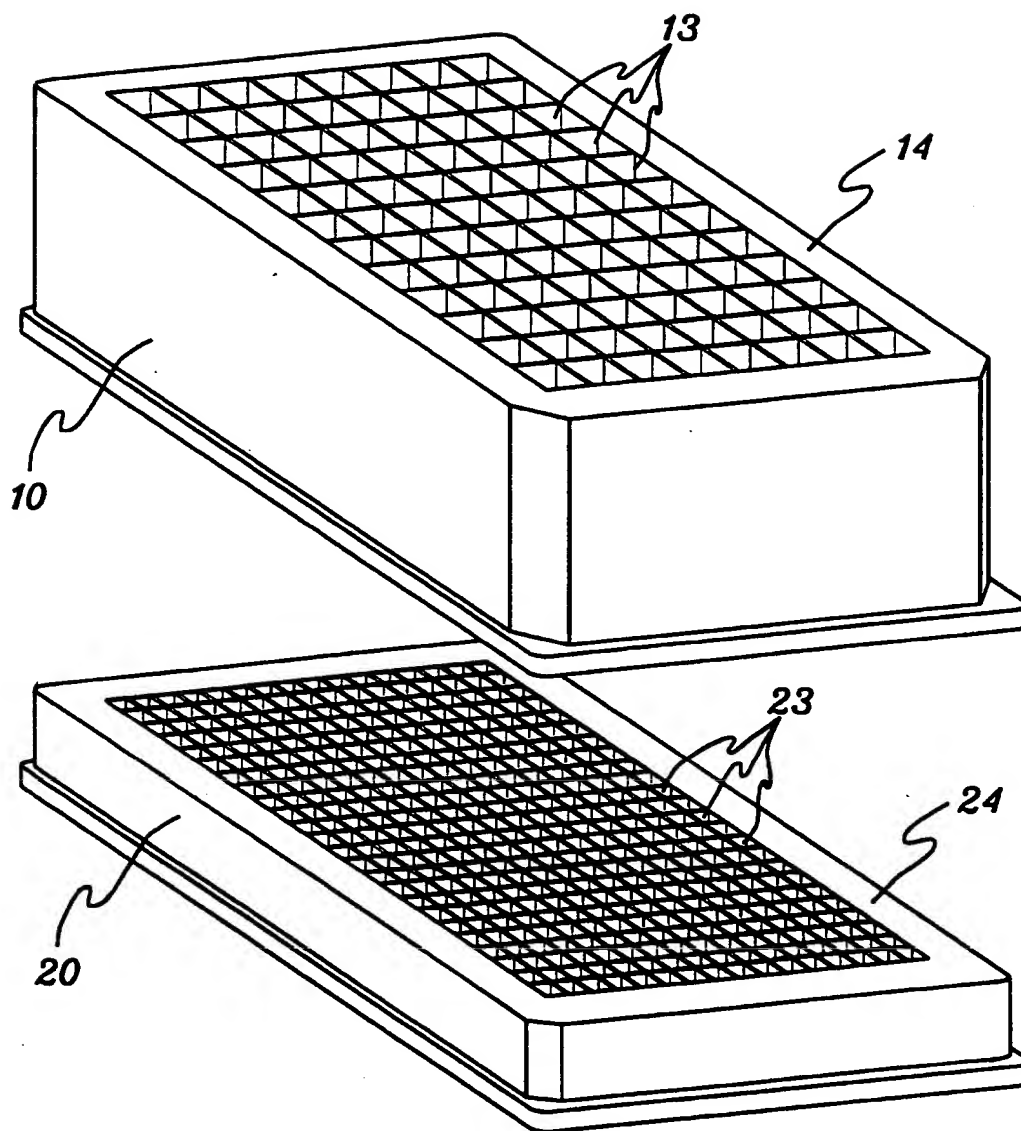
1           67. The method of claim 63, further comprising  
2       creating a seal between the lower surface of said  
3       first multiwell plate and an upper surface of said  
4       second multiwell plate upon said stacking of said  
5       first multiwell plate atop said second multiwell

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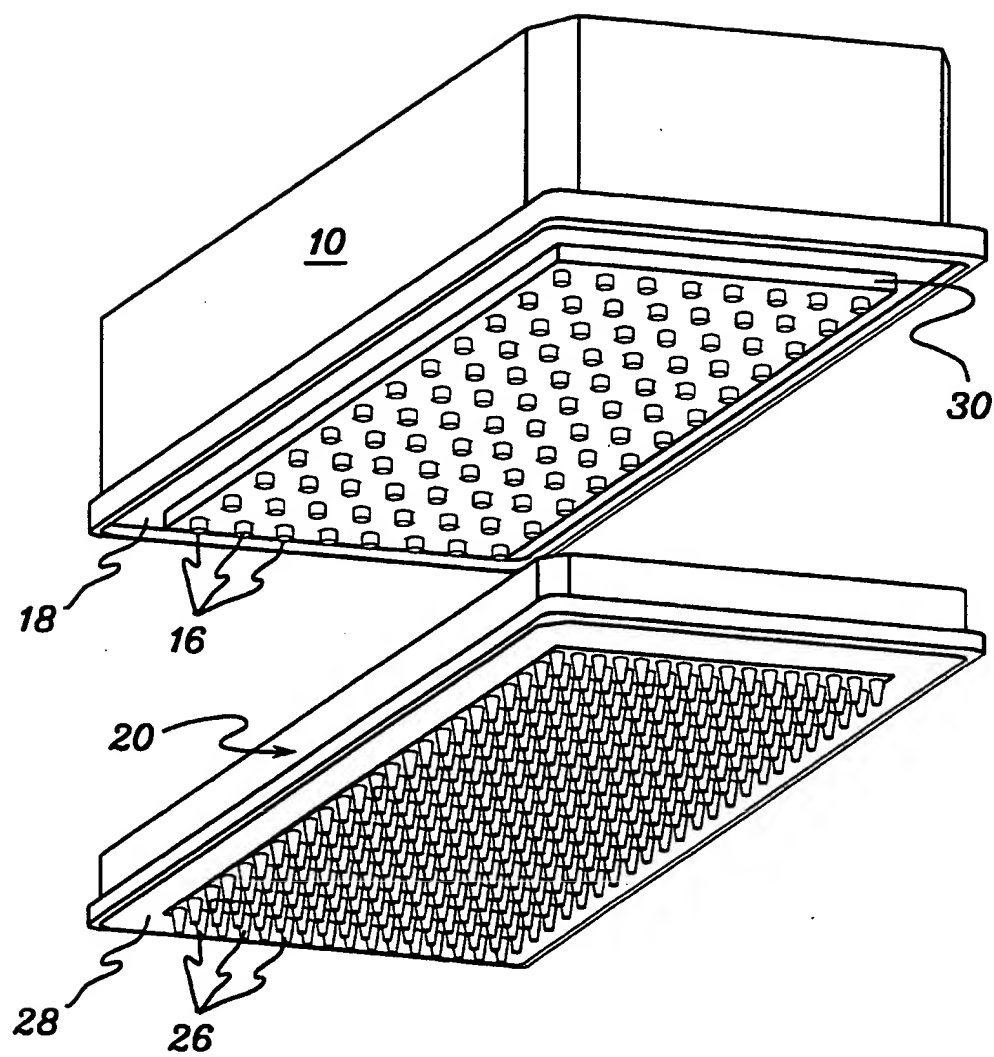
6 plate, said seal preventing cross-contamination  
7 between wells of said second multiwell plate during  
8 said transferring of samples from said first  
9 multiwell plate to said second multiwell plate.

\* \* \* \* \*

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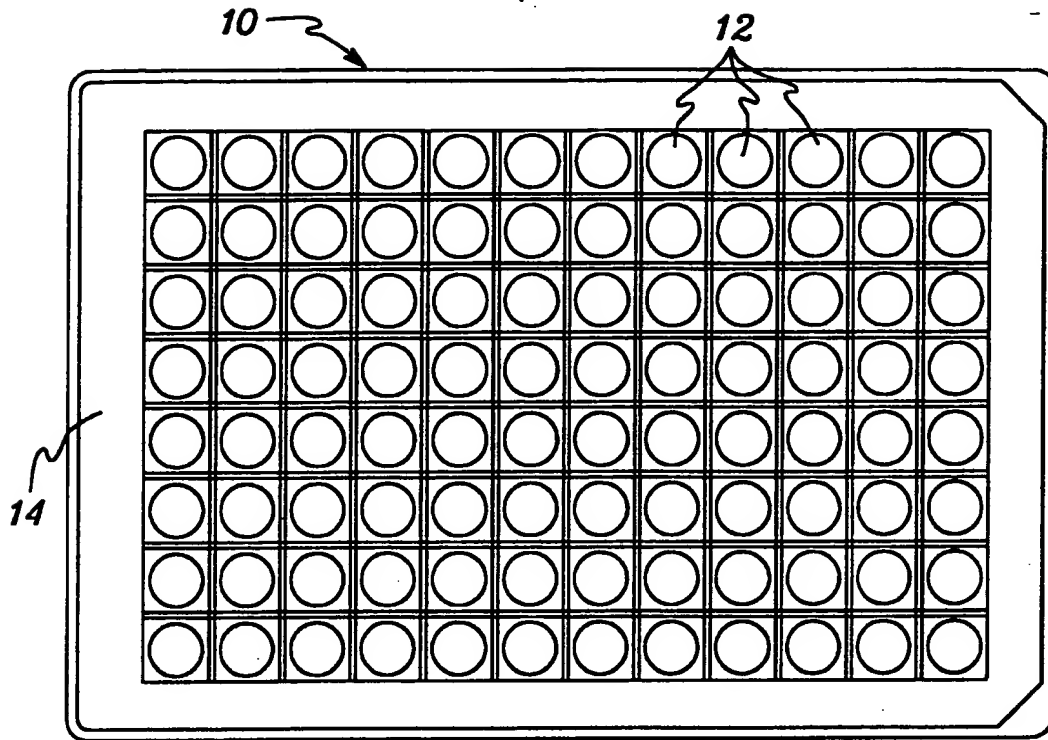
*fig. 1*

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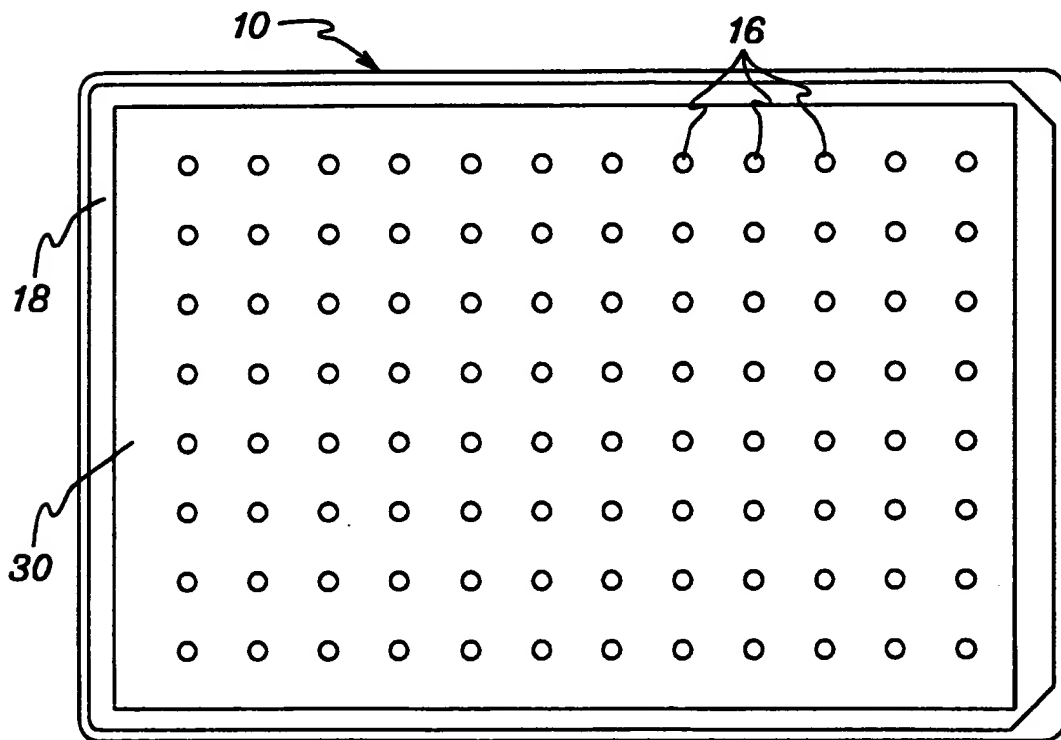
*fig. 2*



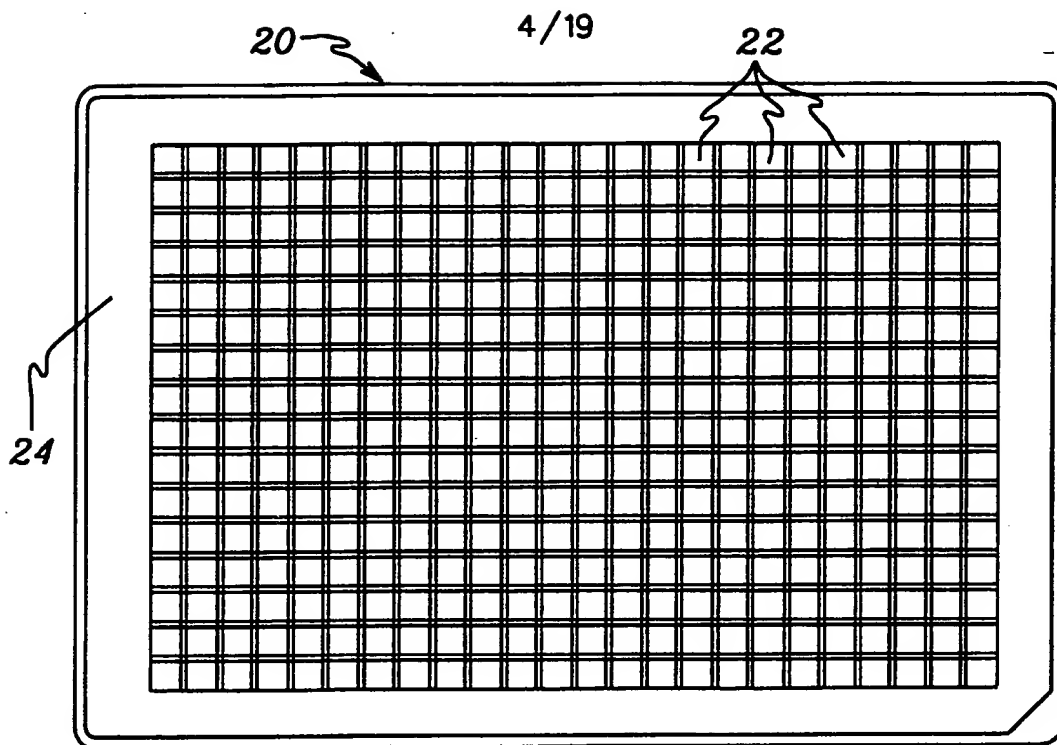
3/19



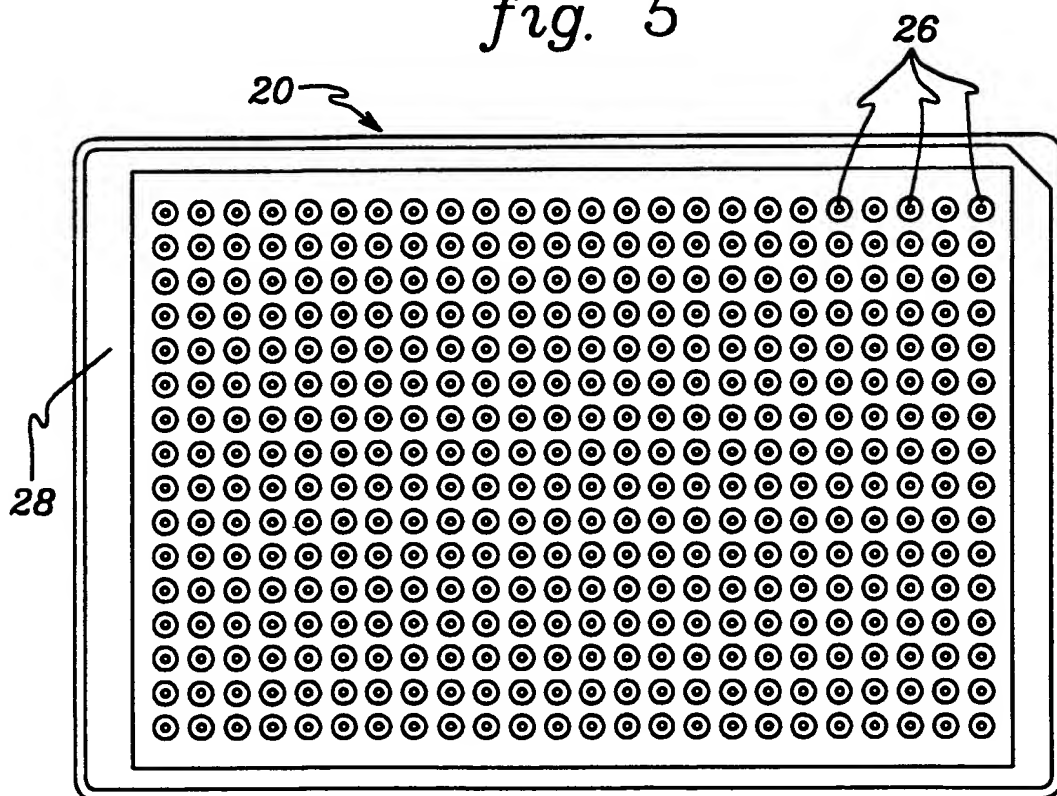
*fig. 3*



*fig. 4*

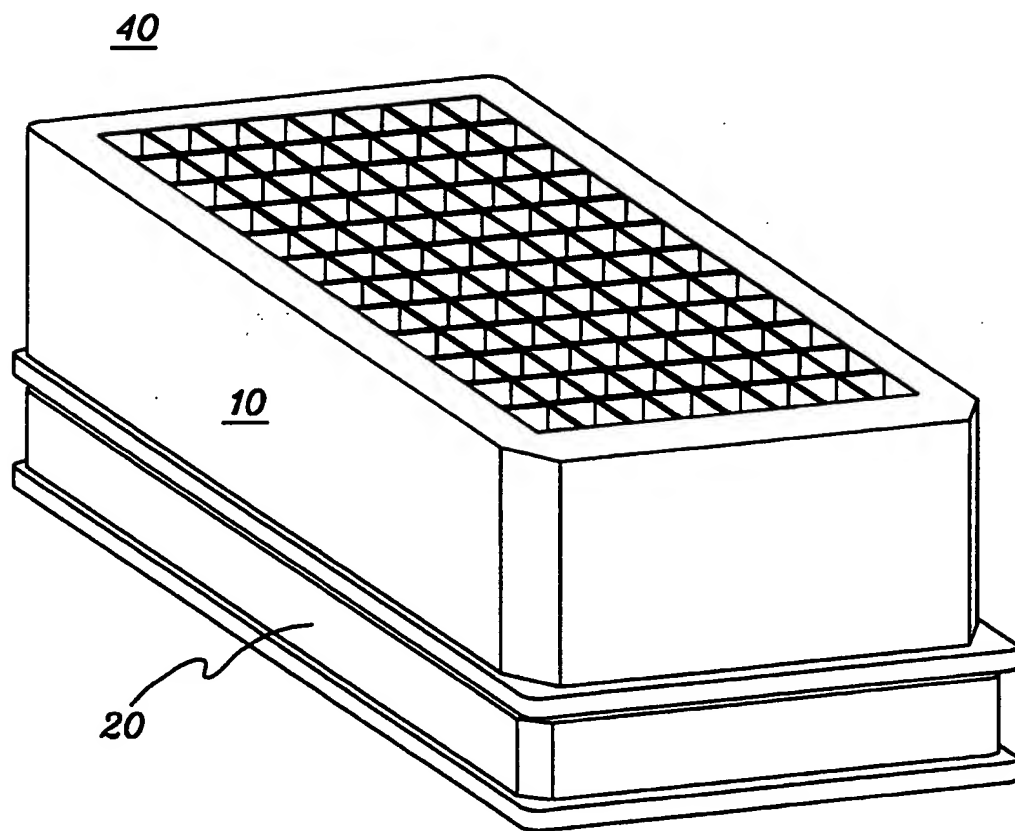


*fig. 5*



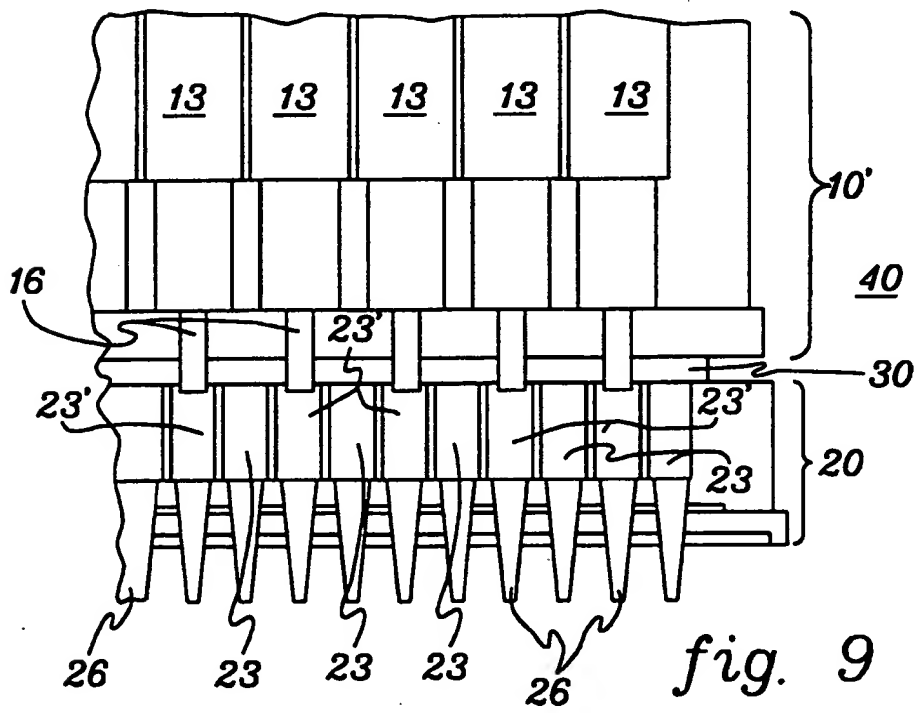
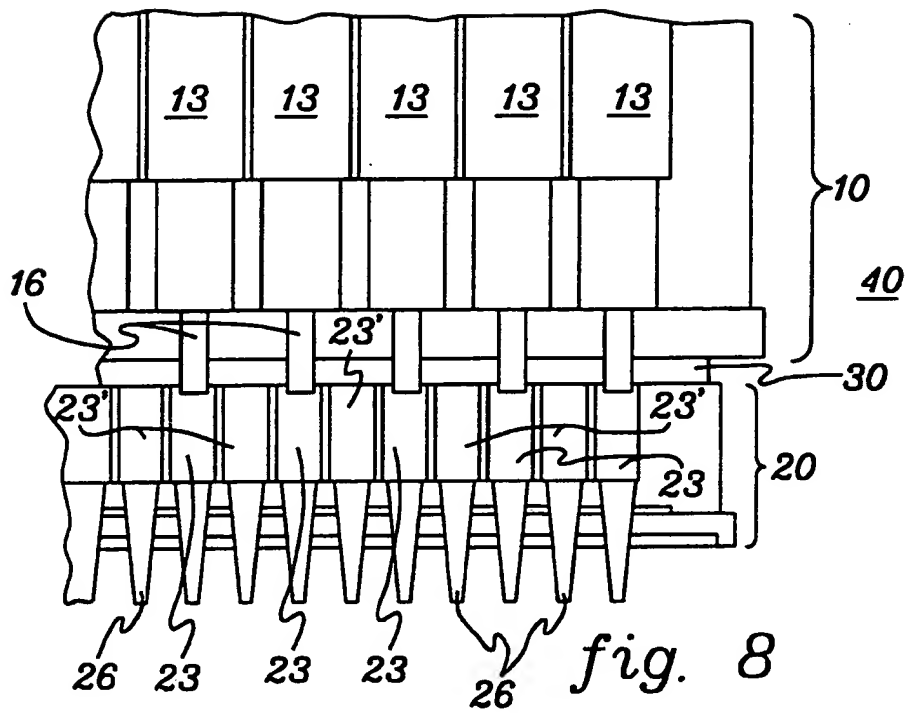
*fig. 6*

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*fig. 7*

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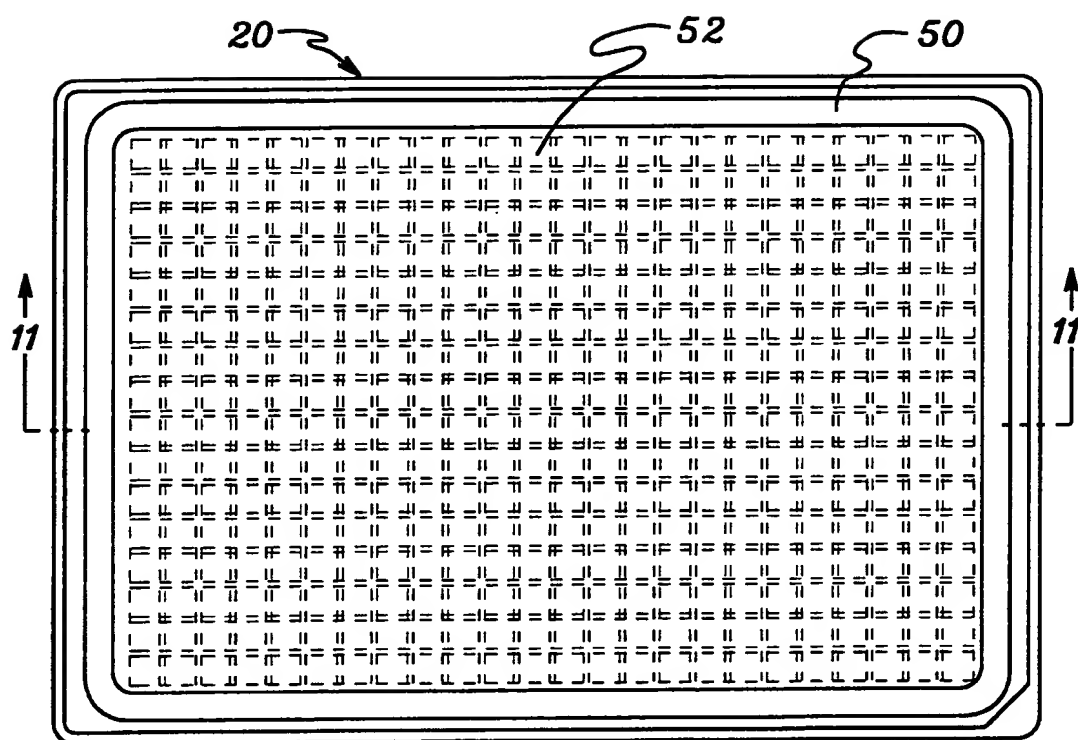


fig. 10

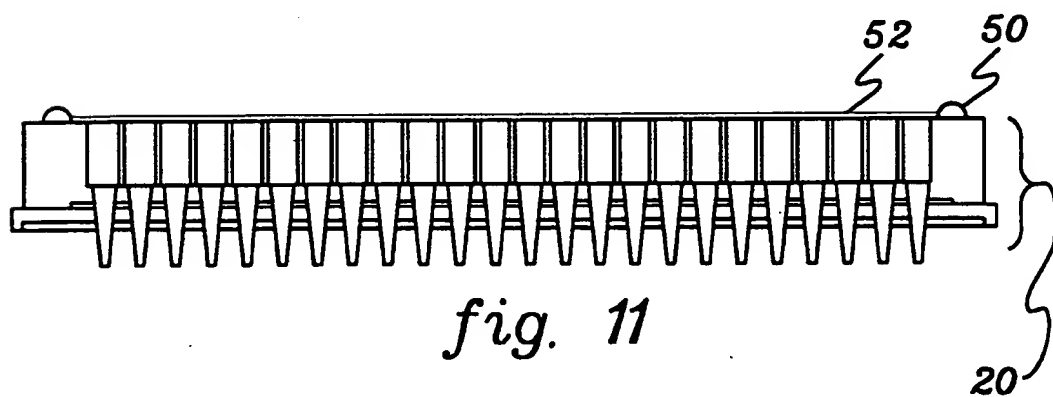
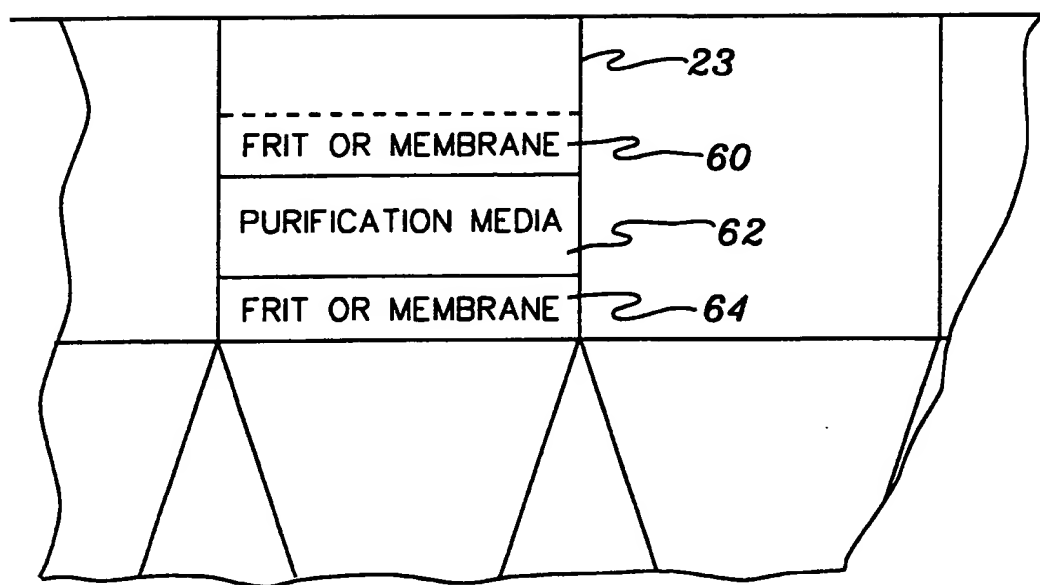
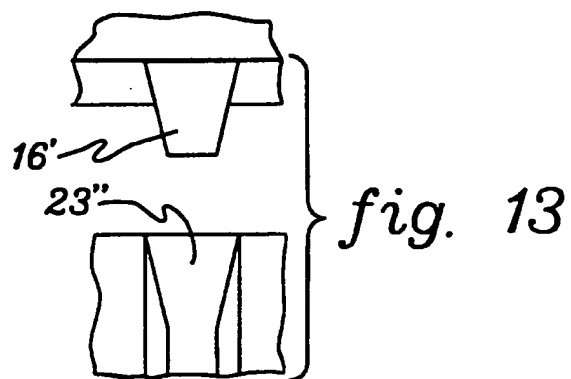
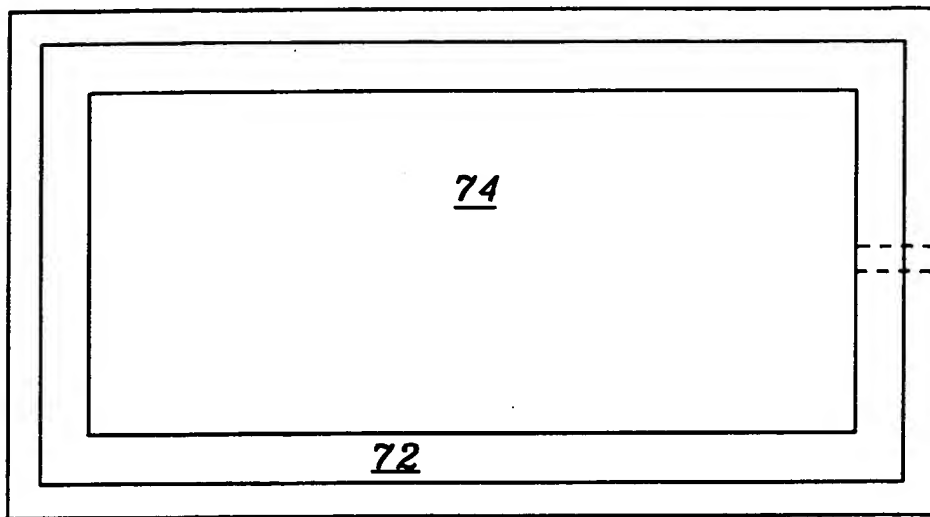


fig. 11

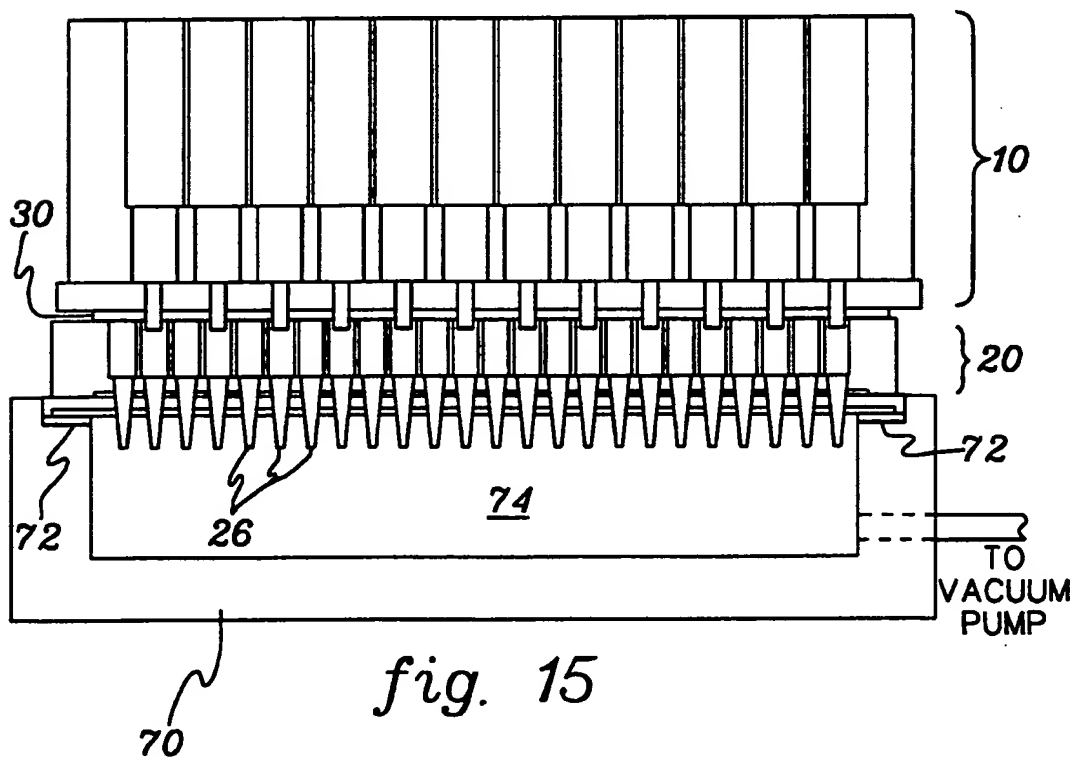
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*fig. 12**fig. 13*

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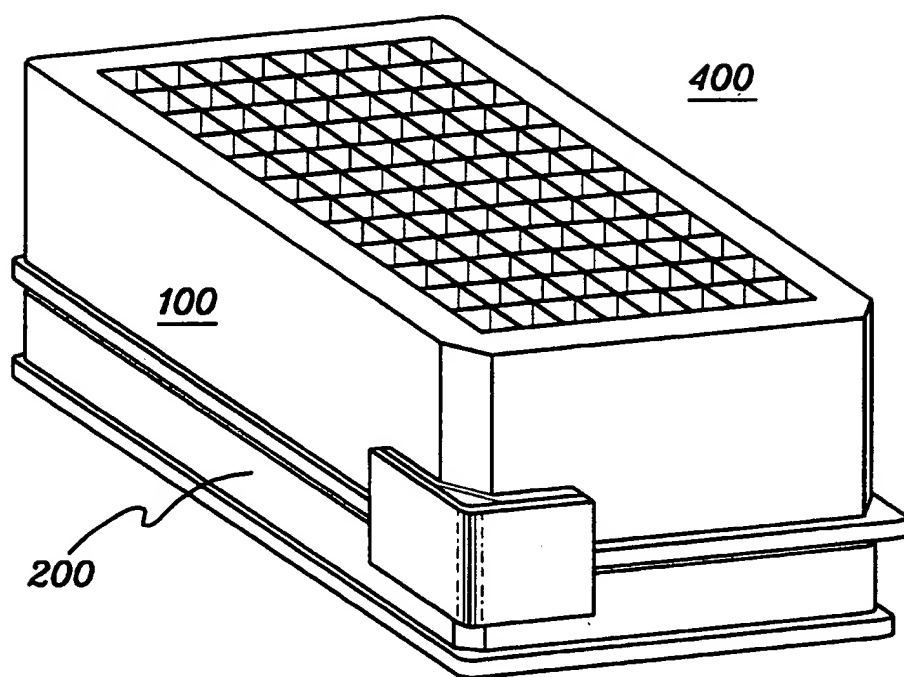


*fig. 14*

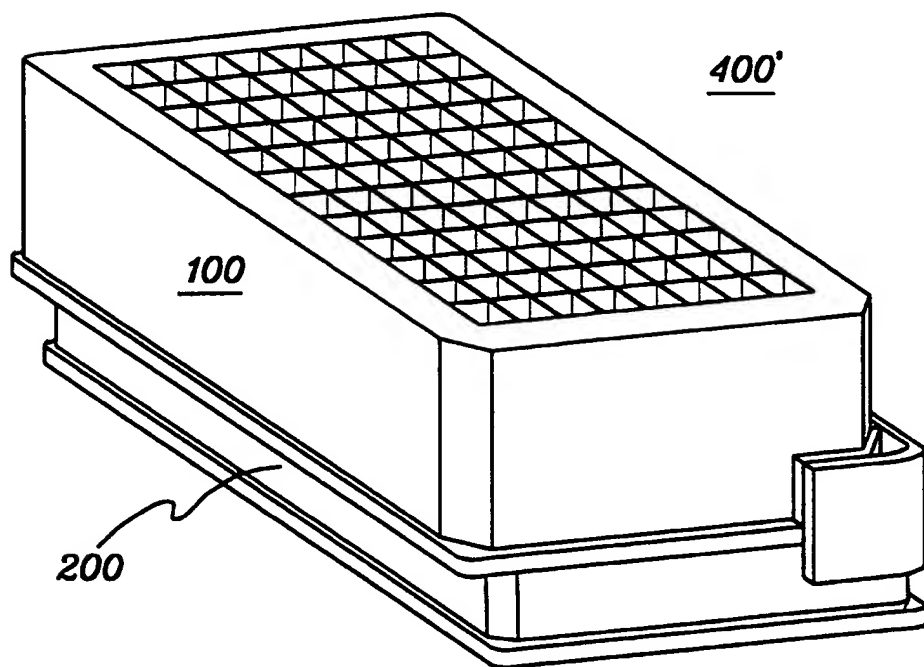


*fig. 15*

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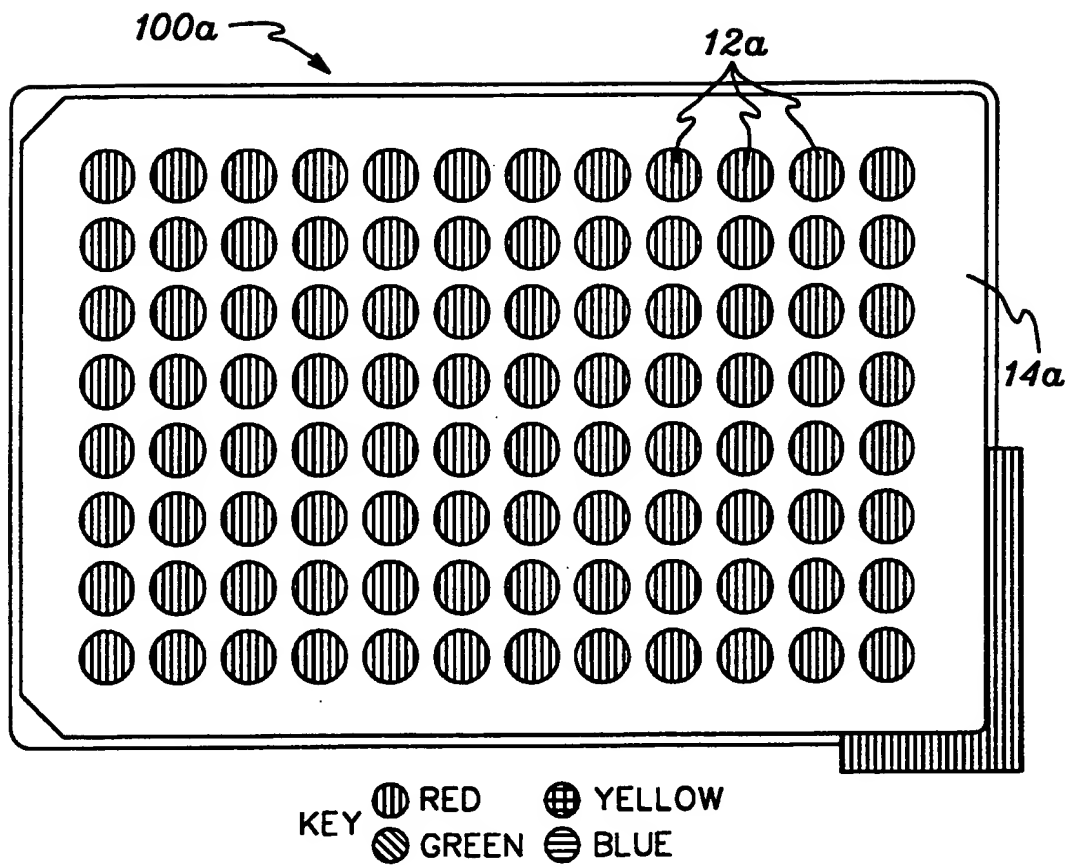
*fig. 16*



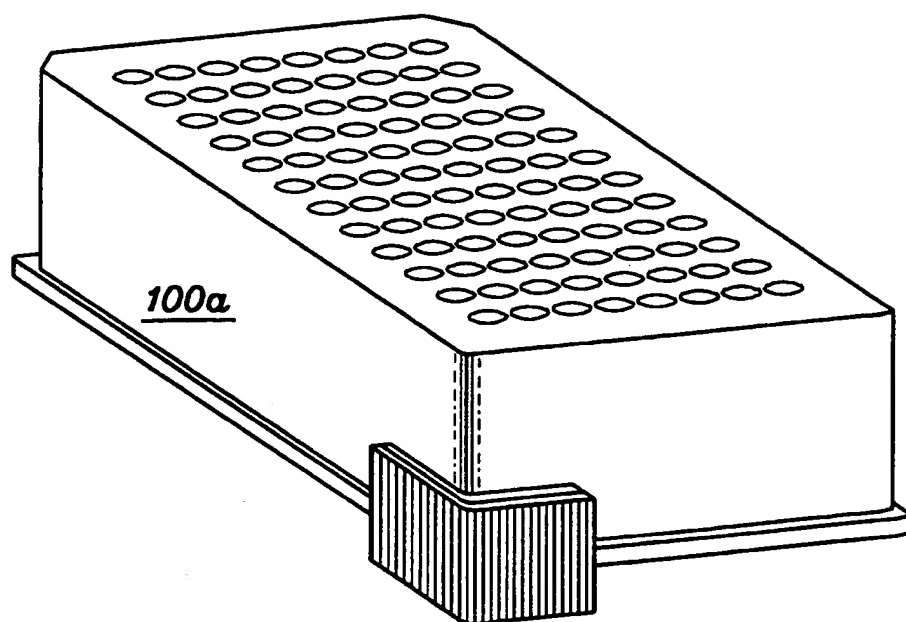
*fig. 17*



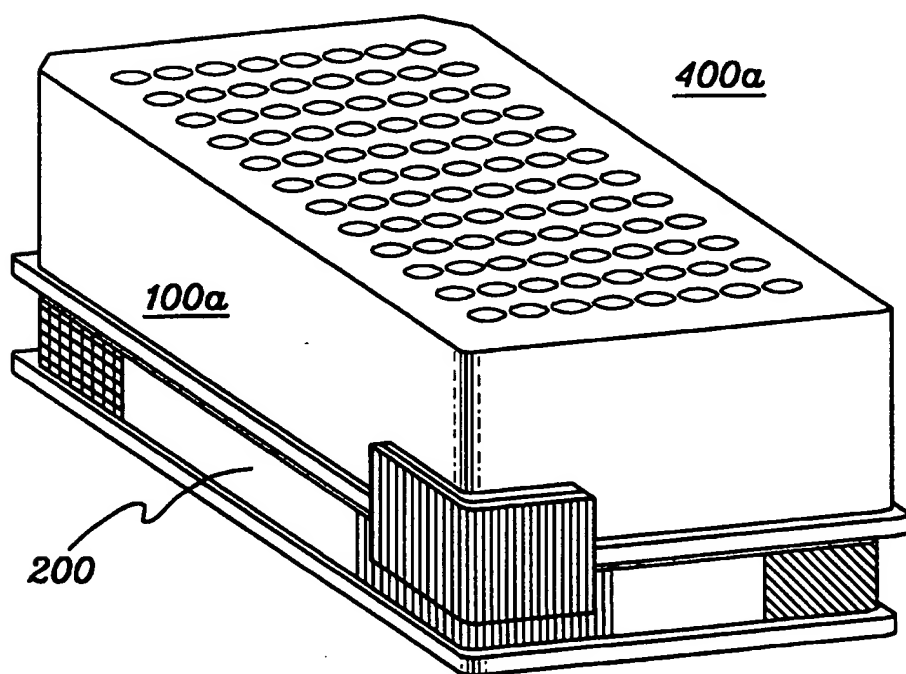
11/19

*fig. 18A*

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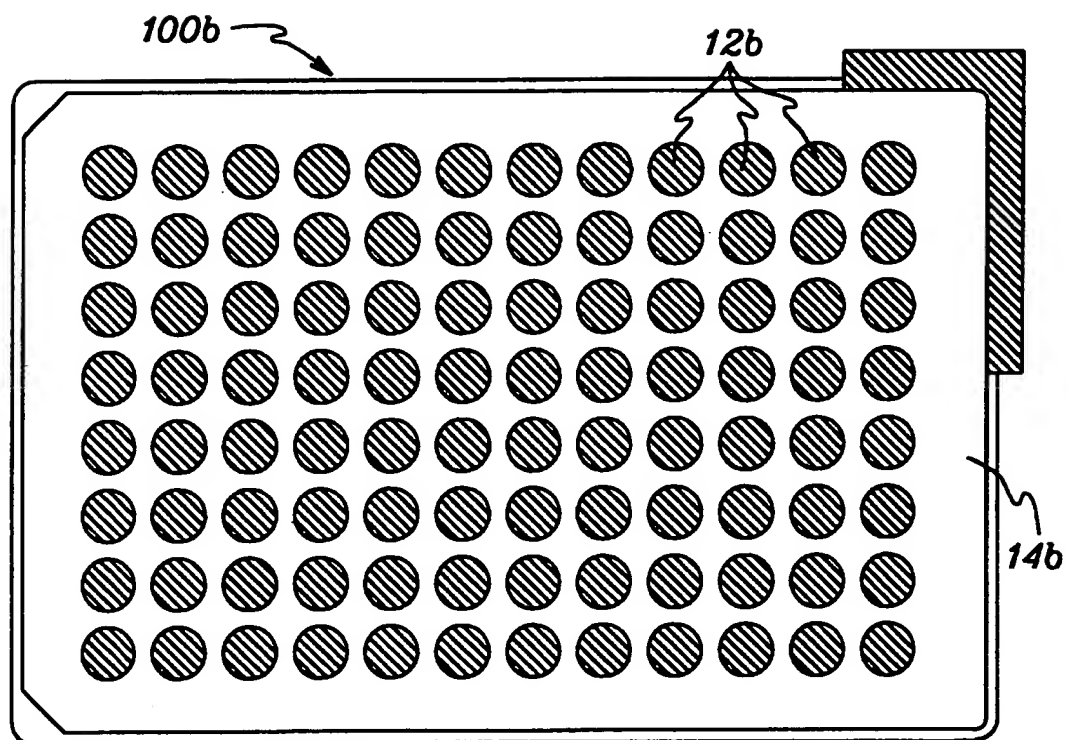


*fig. 18B*



*fig. 18C*

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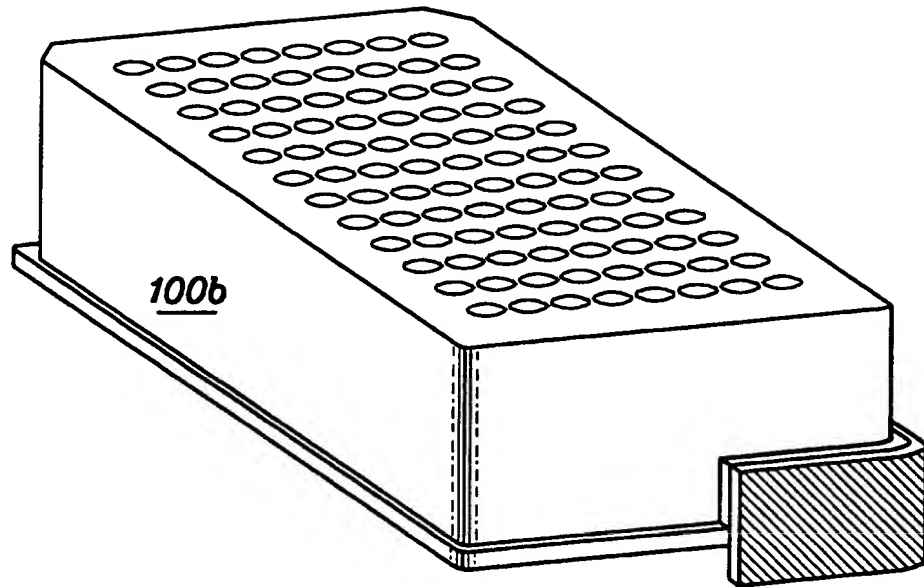


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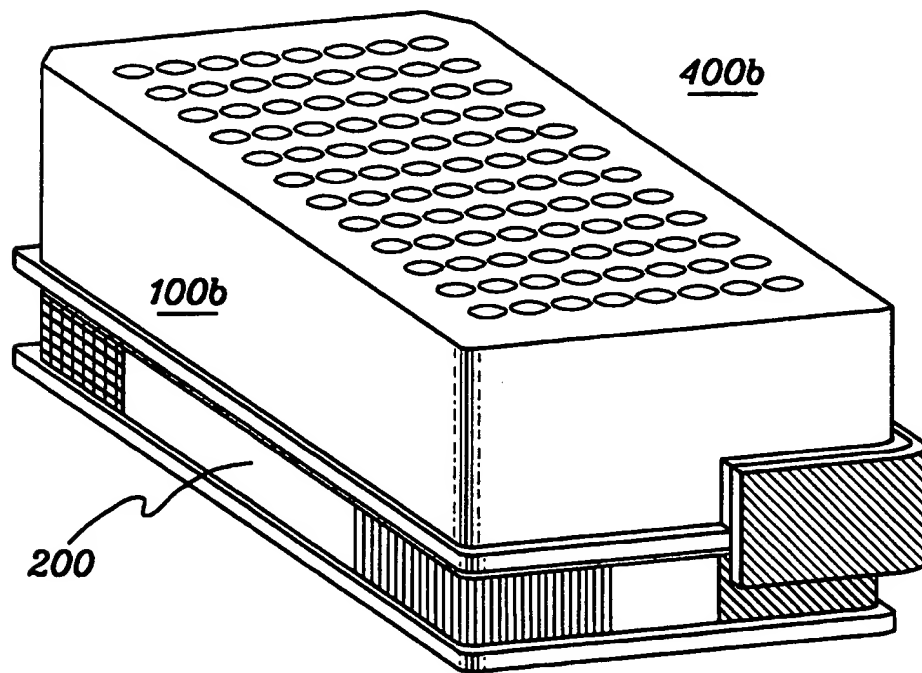
⦶	RED	⦶	YELLOW
⦶	GREEN	⦶	BLUE

*fig. 19A*

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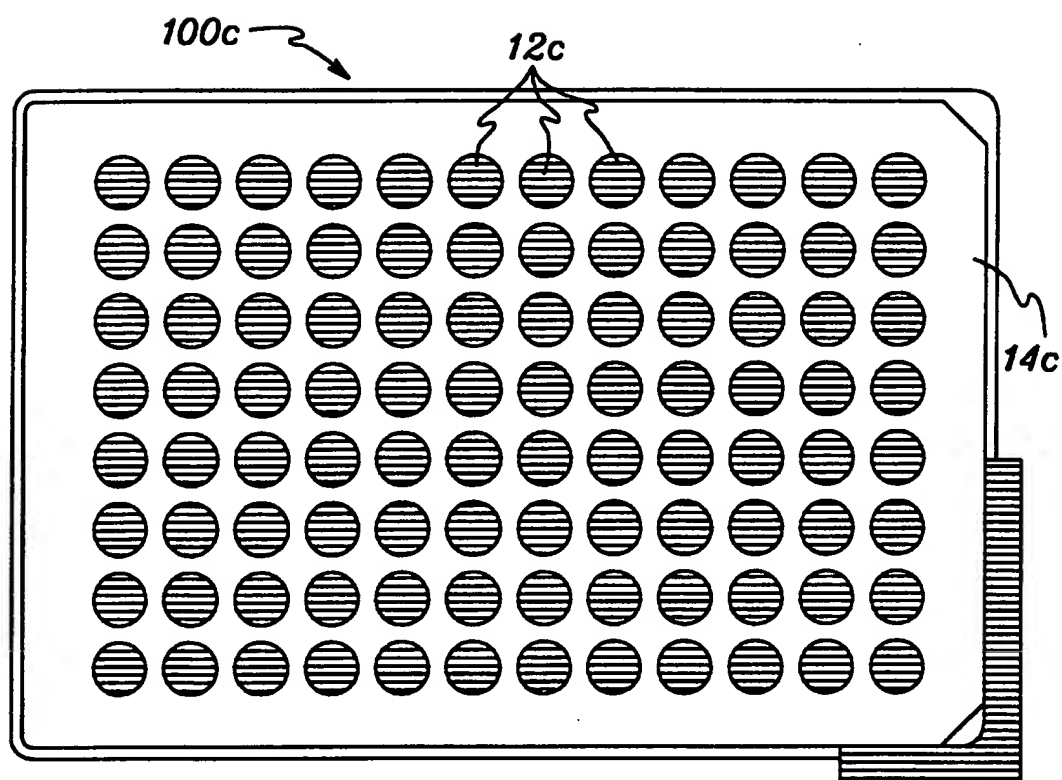


*fig. 19B*



*fig. 19C*

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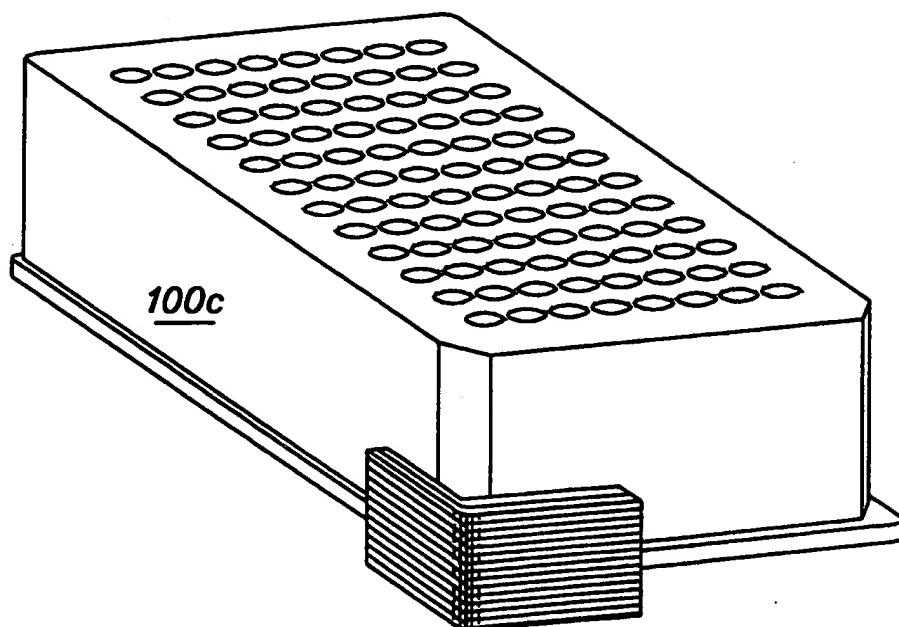


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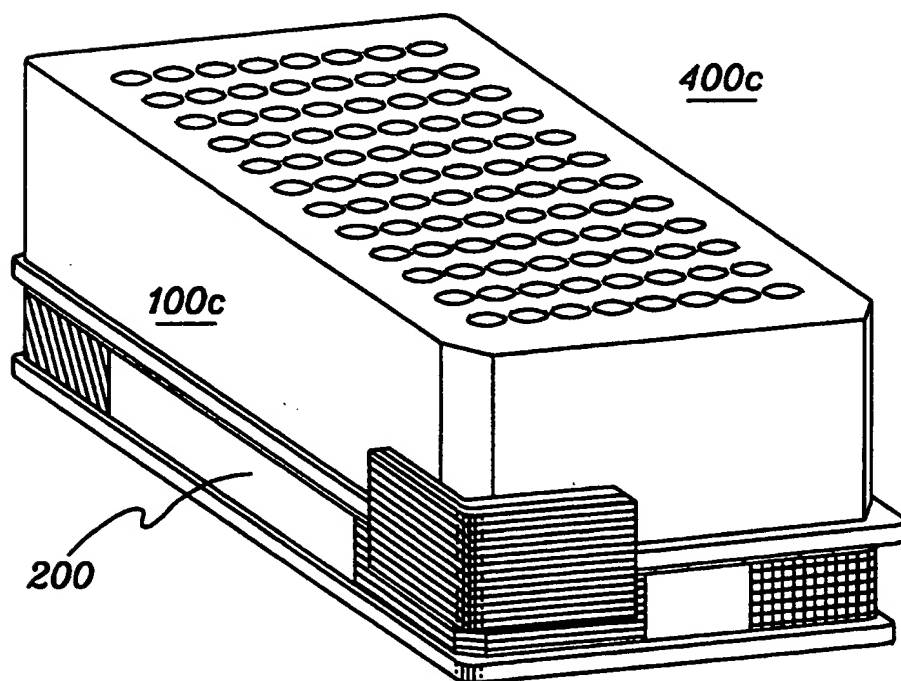
	RED		YELLOW
	GREEN		BLUE

*fig. 20A*

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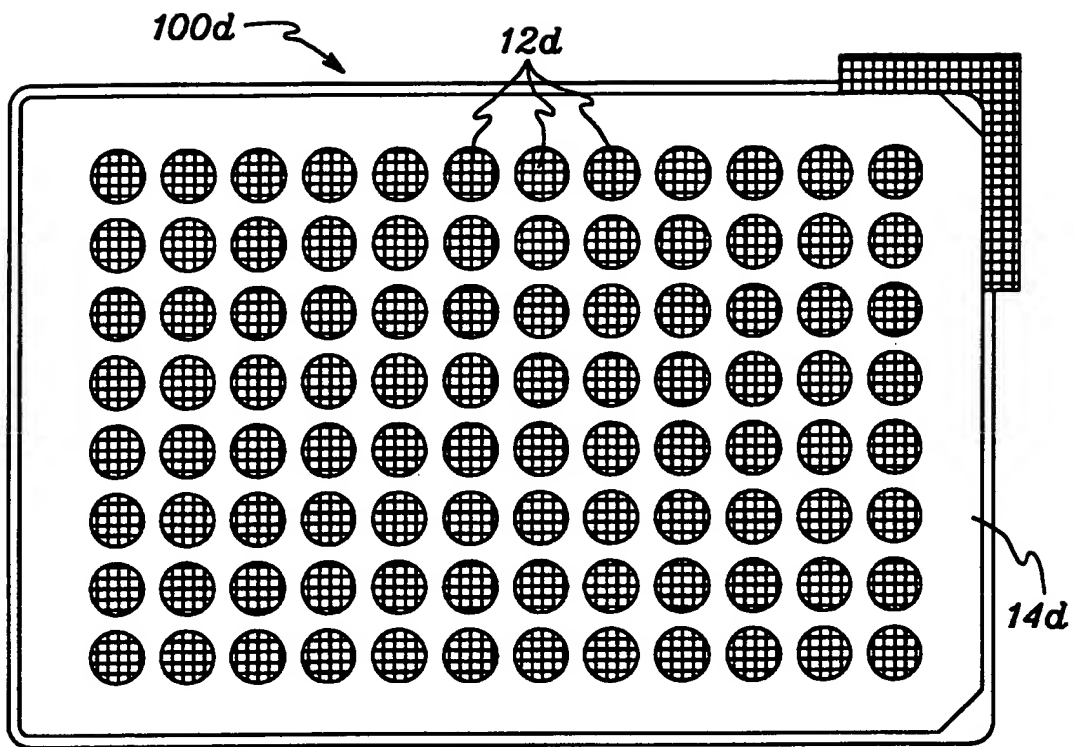


*fig. 20B*



*fig. 20C*

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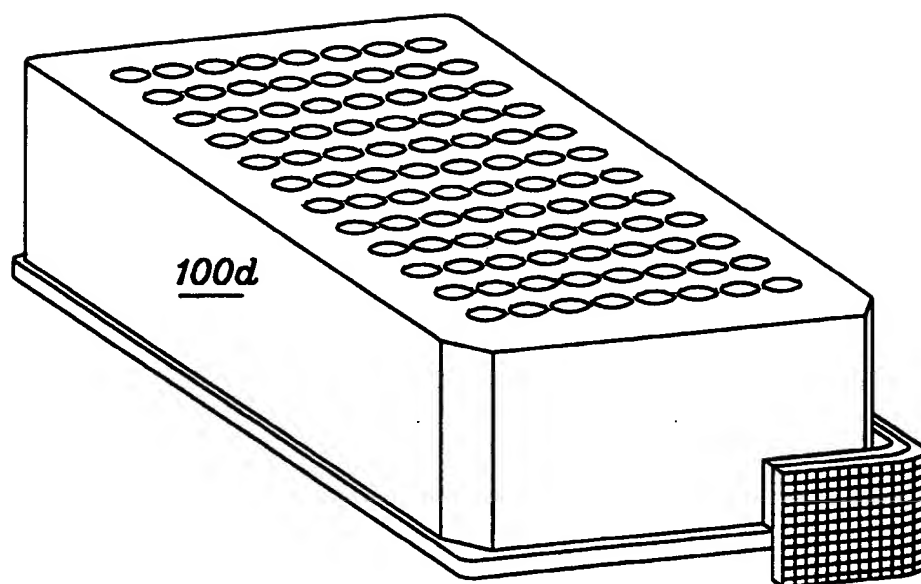


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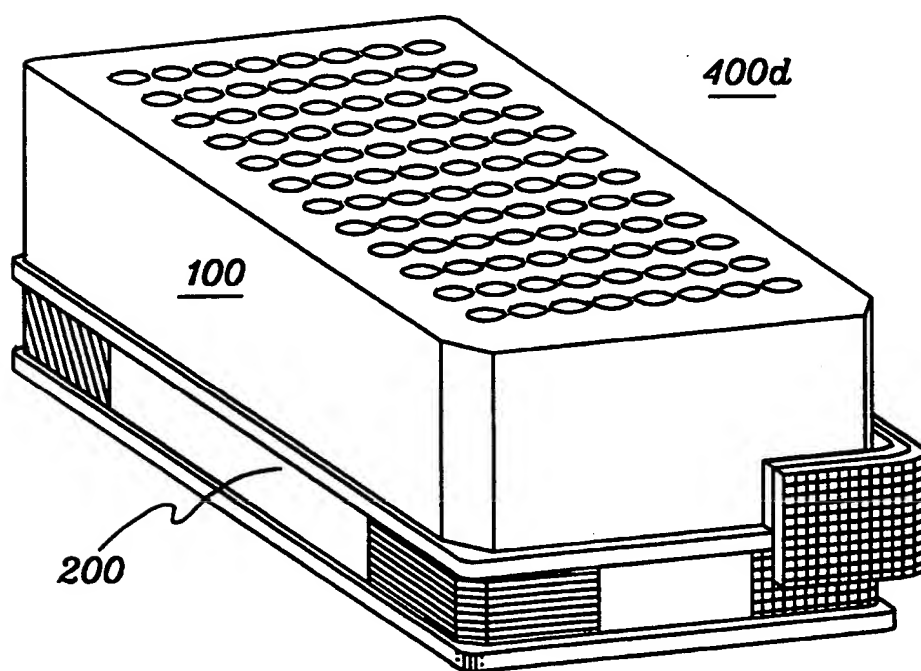
	RED		YELLOW
	GREEN		BLUE

*fig. 21A*

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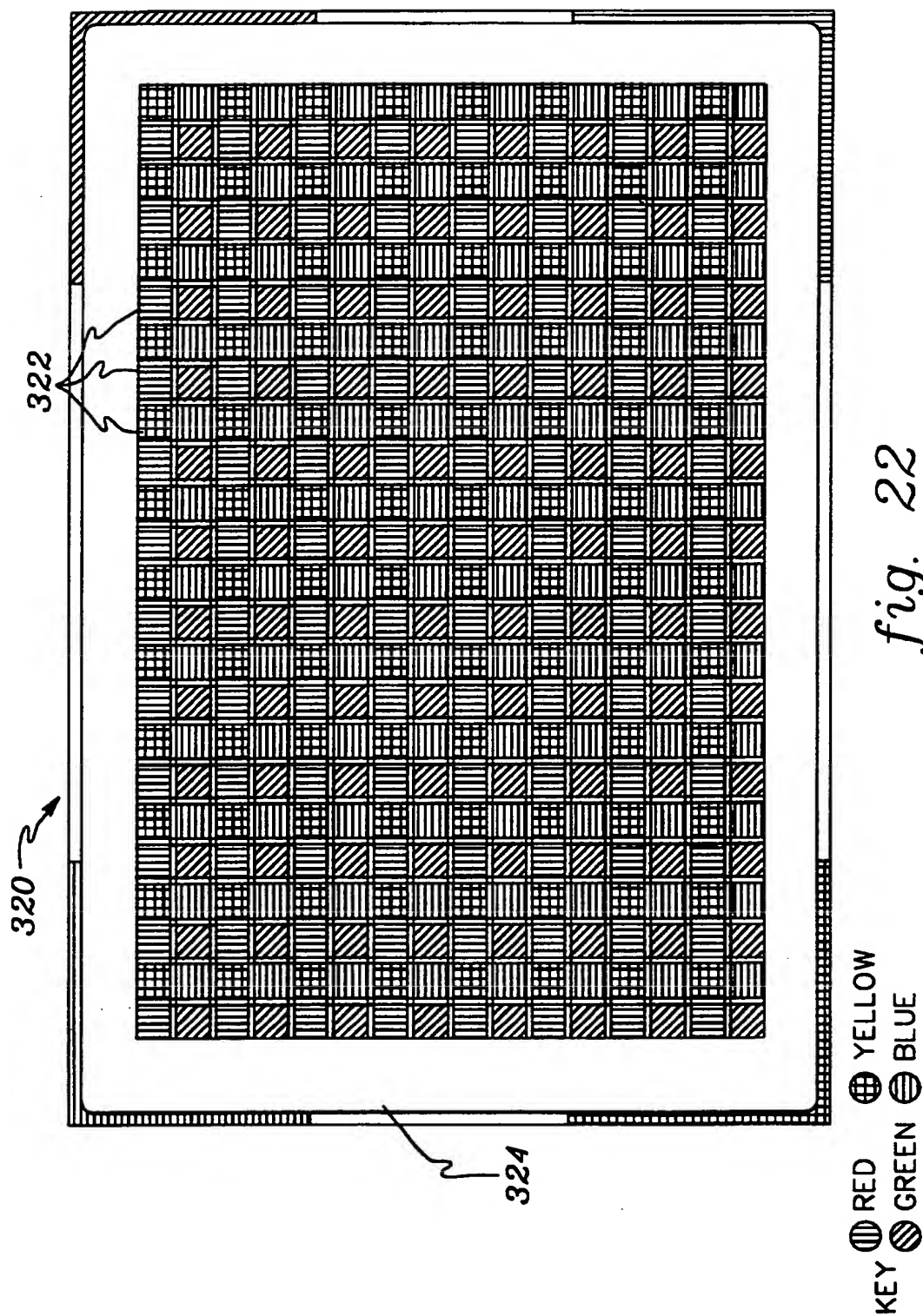
*fig. 21B*



*fig. 21C*



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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/20970

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 B01L3/00 G01N1/00 //C12M1/12,B01D61/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01L G01N C12M C12Q B01D B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 02073 A (PIERCE CHEMICAL CO) 21 February 1991	29, 41-44, 48,60
A	see the whole document ---	11
X	WO 95 27196 A (SANADI ASHOK R) 12 October 1995 see page 1, paragraph 2 see page 5, paragraph 1 - page 6, paragraph 1 see page 19, paragraph 2 - page 20, paragraph 1 see page 22, paragraph 2 - page 23, paragraph 1 see figures 7,9 --- -/--	29,30, 35,36,41

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/20970

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